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Final Report: Tissue Identification by Ultrasound

D. H. LeCroisette
R. C. Heyser
P. M. Gammell
Jet Propulsion Laboratory

R. L. Wilson
Harbor General Hospital
Los Angeles, California

October 15, 1978

Prepared for
National Science Foundation
by
Jet Propulsion Laboratory
California Institute of Technology
Pasadena, California

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PREFACE

The research described in this report was performed by the Earth and Space Sciences Division of the Jet Propulsion Laboratory, California Institute of Technology, and was sponsored by the National Science Foundation (Grant No. APR 75-17388) through an agreement with NASA.

ABSTRACT

A two-year research program has been carried out to measure the ultrasonic properties of animal and human soft tissue over the frequency range of 1.5 to 10.0 MHz. The method employed a swept-frequency, coherent technique known as Time Delay Spectrometry. Measurements of attenuation versus frequency on liver, backfat, kidney, pancreas, spleen, breast and other tissue were made. Considerable attention was paid to tissue handling and in determining the effects of fixing on the attenuation of ultrasound in the tissue.

CONTENTS

I.	Summary	1
II.	Background	2
III.	Time Delay Spectrometry	8
IV.	Equipment Upgrade	16
V.	Transducers	23
VI.	Tissue Handling	27
VII.	Data Handling	30
VIII.	Tissue Measurements	32
	A. Fixed and Fresh Animal Tissue	32
	B. Variation of Attenuation with Frequency	44
	C. Human Tissue Studies	50
	D. Measurements from 1.5 to 17.5 MHz	69
	E. Verification of System Accuracy	70
IX.	Conclusions	72
X.	References	76
XI.	Publications and Presentations	79

Figures

1.	Frequency-Amplitude Spectrum. Upper Curve Is That of Original Pulse. Lower Curve Shows the Spectrum of the Pulse After Undergoing Attenuation of 5 dB MHz^{-1}	7
2.	Time Delay Spectrometry Frequency Sweep	9
3.	Block Diagram of the System	9
4.	Equipment at the Start of the Program	12
5.	Original TDS Ultrasound Instrumentation	13
6.	Block Diagram of the New System	16
7.	In-Phase and Quadrature Component Transforms	18

CONTENTS (CONTD)

Figures

8.	Two Frequency Sweeps from the Original Equipment	21
9.	Polaroid Print of the Output Versus Frequency of the New System	22
10.	Required Specimen Dimensions	29
11.	Time Sequence of Measurements on Hog Tissue	35
12.	Attenuation Versus Frequency Measurements for Hog Pancreas: (a) 6 Hours Post-Mortem (Fresh), (b) 5 Days Post-Mortem (Fresh), (c) 5 Hours Post-Mortem (Fixed), (d) 5 Days Post- Mortem (Fixed)	36
13.	Attenuation Versus Frequency Measurements for Hog Kidney: (a) 3 Hours Post-Mortem (Fresh), (b) 5 Days Post-Mortem (Fresh), (c) 4 Hours Post-Mortem (Fixed), (d) 5 Days Post- Mortem (Fixed)	37
14.	Attenuation Versus Frequency Measurements for Hog Backfat: (a) 1 Day Post-Mortem (Fresh), (b) 6 Days Post-Mortem (Fresh), (c) 1 Day Post-Mortem (Fixed), (d) 6 Days Post- Mortem (Fixed)	38
15.	Attenuation Versus Frequency Measurements for Hog Liver: (a) 5 Hours Post-Mortem (Fresh), (b) 5 Days Post-Mortem (Fresh), (c) 5 Hours Post-Mortem (Fixed), (d) 5 Days Post- Mortem (Fixed)	39
16.	Band Diagram of Attenuation Versus Frequency for Hog Pancreas	40
17.	Band Diagram of Attenuation Versus Frequency for Hog Pancreas	41
18.	Band Diagram of Attenuation Versus Frequency for Hog Backfat	42
19.	Band Diagram of Attenuation Versus Frequency for Hog Liver	43
20.	Attenuation Versus Frequency at Four Different Temperatures in Hog Backfat	49
21.	Attenuation Versus Frequency at Four Different Temperatures in Hog Liver	51
22.	Attenuation Versus Frequency at Three Different Temperatures in Hog Spleen	52

CONTENTS (CONTD)

Figures

23.	Attenuation Versus Frequency at Three Different Temperatures in Hog Kidney	53
24.	Measurement of Attenuation Versus Frequency for an Excised Breast Specimen	54
25.	Measurement of Attenuation Versus Frequency in Breast Tissue	55
26.	Attenuation Versus Frequency for a Metastatic Tumor of the Breast at 38°C	56
27.	Attenuation Versus Frequency in Leukemic Human Spleen at 37°C. Average of Three Readings. Error Bars Show Standard Deviation. (a) Unfixed Specimen, (b) Same Specimen After Formalin Fixation	57
28.	Attenuation Versus Frequency in a Human Pancreas	58
29.	Effect of Fixing on Abdominal Fat	59
30.	Effect of Fixing on a Liver Specimen	60
31.	Effect of Fixing on an Acute Fatty Liver	61
32.	Early Measurements of Attenuation Versus Frequency at Two Temperatures on a Fatty, Cirrhotic Liver	62
33.	Attenuation Versus Frequency as a Function of Temperature on a Normal Liver (Average of Seven Readings)	63
34.	Attenuation Versus Frequency as a Function of Temperature on a Fatty Liver (Average of Nine Readings)	64
35.	Attenuation Versus Frequency as a Function of Temperature in a Cirrhotic Liver (Average of Nine Readings)	65
36.	Attenuation Versus Frequency as a Function of Temperature in a Second Cirrhotic Liver (Average of Five Readings)	66
37.	Attenuation Versus Frequency as a Function of Temperature in a Third Cirrhotic Liver (Average of Five Readings)	66
38.	Variation in Attenuation with Temperature for a Cirrhotic Liver. Readings Taken on the Same Liver as Figure 36 After It Had Been Formalin Fixed	67
39.	Measurement of Attenuation Versus Frequency on Hog Specimens Over Range 1.5 to 17.5 MHz	69

CONTENTS (CONTD)

Figures

40. Comparison of Measurements on Castor Oil Taken on the TDS
System With Data of Other Investigators 71

Table

1. Values of Acoustic Reflection Coefficient 5

I. SUMMARY

Research has been carried out at the Jet Propulsion Laboratory of the California Institute of Technology to measure the ultrasonic properties of animal and human soft tissue over the frequency range of 1.5 to 10.0 MHz. This program was funded by the National Science Foundation.

The aim of this work was to obtain fundamental information on the effects of normal and pathological soft tissue on the propagation of ultrasonic energy. In the last twenty years, pulse-echo ultrasonic devices have been increasingly used as a diagnostic tool in medicine. Most of the diagnostic information has been obtained by observing the tomographic image showing the location of tissue boundaries that is displayed on a cathode-ray tube. An experienced clinical ultrasonographer has been able to interpret the images on the screen by correlating the patterns with the known anatomy and suspected pathology of the patient. This work was designed to obtain fundamental information on tissue ultrasonic parameters that would be useful in interpreting the clinical images. For example, it has been found that some measurable properties of tissue, such as the variation in attenuation of sound as a function of frequency, can be used to differentiate between normal and pathological tissue. The fundamental measurements reported here will be of value in elucidating the mechanism of the interaction between the mechanical energy and the tissue and also in interpreting the medical images.

The method employed a swept-frequency coherent measurement technique known as Time Delay Spectrometry. Measurements on liver, backfat, kidney, spleen, breast and other tissue were made. Considerable attention was paid to tissue handling and in determining the effects of formalin fixing on the attenuation of ultrasound in tissue.

II. BACKGROUND

On July 1, 1975 the principal investigator submitted a proposal entitled "Tissue Identification by Ultrasound" to the National Science Foundation. The proposed work was a series of measurements on animal and human tissue using ultrasonic energy as an investigative tool to differentiate between normal and pathological tissue.

In the last twenty years, pulse-echo electronic devices have been used increasingly as a diagnostic tool in medicine. These units are non-invasive, relatively inexpensive and present no known hazard to the patient. Most of the diagnostic information is obtained from a tomographic image which shows the location of tissue boundaries that is displayed on a cathode-ray tube (CRT) screen. The principal medical specialties using this equipment are obstetrics, cardiology, internal medicine and ophthalmology.

The majority of ultrasound imaging instruments operate in the B-mode with compound scanning. In this type of system a probe is moved in one plane around the patient. The reflection from any tissue-to-tissue interface in the body is plotted on a cathode-ray tube and the resulting picture is photographed. To overcome the problems caused by the fact that reflection in the body is substantially specular, the transducer is rocked about the position where it is normal to the surface. Thus the internal tissue boundaries will be illuminated at several different angles as the probe is moved to new positions. This action, which is known as compound scanning, produces more complete mapping since there is a higher probability of a reflection occurring from a given tissue interface during compounding than if the transducer were always held normal to the surface of the body.

Whatever the transducer motion, or however the imaging on a screen is carried out, the basic ultrasonic systems rely upon the concept of using a pulsed source, a discrete reflector and a time-selective receiving system. By analogy with early radar and sonar units, this is a straightforward and sensible way to produce position mapping. Commercial pulse-echo systems now in use are reaching the current limits set by the fundamental physics of the transducer polar diagrams (spatial beam width), the feasible pulse time durations, and the processing and display capabilities.

The B-scan tomographic system provides a map of organ or tumor interfaces. The image information is commonly displayed as a gray-scale image on the CRT. In many cases this image can provide enough information for a satisfactory diagnosis. This is particularly true where, for example, a tumor is observed that is sufficiently large so that its outline can be discerned or it displaces neighboring organs in a detectable manner. This is not always the case, however, and it is obviously desirable to be able to detect and identify smaller tumors whose space-occupying pathology has not yet manifested itself. In addition, the ability to measure specific structural features or to obtain pathological information from an ultrasound system would greatly increase the utility of this modality. The aim of the work, therefore, was to obtain fundamental information that would allow a better understanding of tissue properties as measured by ultrasound. The long-term goal is the improvement of the diagnostic capability of future instrumentation.

Data on the attenuation of soft tissues are scarce and, in some cases, results reported in different studies are conflicting. Furthermore, because of major problems of measurement, the relative values of absorption and scattering, which together constitute attenuation, are almost unknown. Until recently there had not been a major compilation of these data since the paper by Goldman and Heuter (1) in 1956. At the present time, however, a new review has been carried out by F. Dunn and co-workers at the University of Illinois (2).

The pulse-echo ultrasonic system has been suggested as a means of diagnosing the nature of lesions in human tissue since it first came into use in medicine. The work of Wild and Reid which has been reviewed in Wells (5) was the first discussion of diagnosis, as distinct from imaging, of lesions in tissue. They used a 14 MHz system and an A-scan display to show there were quantitative differences between malignant and benign tissue. Back-scattered sound from one breast with assumed pathology was compared with normal echoes from the same region of the opposite breast. A greater return was found from malignant regions. The measurement was made by comparing the A-scan echographic ratio (area under the curve) among malignant, benign and normal tissue. The equipment had a range of only 0.5 to 1 cm.

If the tumor was deep the probe was pushed into the breast and the fat moved out of the way as much as possible. There were few attempts to follow this until the 1970's when a revival of interest in tissue identification occurred.

Since 1950 great advances have been made in the development of commercial ultrasound equipment for use in the clinic and the number of physicians using ultrasonic imaging devices for diagnosis has increased rapidly. As a result of this, a vast number of images has been studied by trained observers in hospitals around the country and the world. Features have been found in the images which correlate with the pathological state of the tissue. The basis for the diagnosis is usually subjective; after reviewing hundreds of images an ultrasonographer can identify and categorize certain features that correspond with particular pathological states. This is the stage that tissue characterization has reached at the present time.

A signature has been defined by Le Croisette and Heyser (3) to be:

"The set of identifiable properties or attributes that places one thing apart from another".

Thus, a signature may be comprised of any type of data which is sufficient to uniquely identify the tissue.

The major ultrasonic property that is used to provide informational content in an ultrasonic image is the reflectivity. The reflection of ultrasound from a boundary depends upon the values of the specific acoustic impedances of the tissue on the two sides of the border. The specific acoustic impedance is given by:

$$Z = \rho c$$

where ρ is the density and c is the velocity of sound in the medium.

For unbounded longitudinal waves traveling in a medium of acoustic impedance Z_1 and normally incident on an infinite plane surface, with a medium of acoustic impedance Z_2 , the pressure amplitude reflection coefficient, R , is:

$$R = \frac{Z_2 - Z_1}{Z_2 + Z_1}$$

Typical values of the reflection coefficient are given in Table I.

	Muscle	Liver	Blood
Fat	0.067	0.049	0.047
Muscle		0.015	0.020
Liver			0.028

Table I. Values of Acoustic Reflection Coefficient

The reflection coefficient at the interface between bone and any soft tissue is just greater than 0.5. Furthermore the attenuation of ultrasound in bone is much higher than in soft tissue. The combination of these two factors results in a high reflected pulse from a bone interface and a reduction of information content behind the bone. This is known as acoustical shadowing. In soft tissue, as seen from the limited information given in Table I, a reflection coefficient of a few percent is typical. These echoes are the basis for the method. The B-scan image is obtained by displaying these pulses on the screen in relative position of the location of the reflecting surface of the body. The image obtained shows the location of organs and other features of the body.

The pulse-echo system has been of great value in locating boundaries between tissue types. A typical pulse of 2.25 MHz ultrasonic energy lasts for less than 1 microsecond and provides a positioning accuracy in the longitudinal direction (along the beam) of a few millimeters. In the lateral direction (at right angles to the beam), the resolution is determined by the size of the transducer and whether or not focussing is used. The resolution is typically poorer in the lateral direction than longitudinally. This effective resolution of a few millimeters in size is adequate for the diagnostic techniques to be very effective.

As the use of the modality has grown there has been an awareness of the strengths and weaknesses of the technique. This research group has approached the question of tissue identification by considering some of the signal processing aspects of characterization. In order to distinguish one tissue from another, it is necessary to be able to identify characteristics in the signature that can be correlated with the type of status of the tissue. In the current pulse-echo system as presently available, the signal processing through the system allows very few signal characteristics to be retained in the final image.

In a system which displays a gray-scale image, there is amplitude information on the echo returns but nothing more. Any changes in shape of the returning pulse, indicating frequency or phase changes in transit or upon reflection, are lost. Furthermore, signal shaping to give some edge enhancement occurs in most units. The emphasis is placed on producing a clear, sharp picture even at the expense of losing information.

The shape of the transmitted pulse is mainly determined by the characteristics of the transducer. Transducers are made with high damping and the resulting "Q" is between 2 and 3. At the typical frequency of about 2.25 MHz, this produces an output pulse of ultrasonic energy of duration between 0.5 and 1.0 microseconds containing 1 1/2 to 3 cycles.

There is no direct control exercised over the frequency spectrum of the emitted pulse. Since the primary object in current pulse-echo systems is time discrimination, the transducer is heavily damped to produce a short pulse and the frequency bandwidth follows. The values found in medical ultrasound systems have been measured by Redwood (4) and discussed by Wells (5). The upper curve in Figure 1 shows a typical value.

When sound travels through soft tissues it suffers attenuation which is a function of frequency. The lower curve in Figure 1 shows the frequency spectrum of a pulse after being attenuated by 5 dB MHz^{-1} , which is the attenuation typically experienced by a sound wave travelling from the transducer to an interface at a range of 5 cm and back to the transducer. The greater the attenuation, the higher the relative reduction in the high frequency components. In the time domain, the pulse broadens and its amplitude decreases. In current pulse-echo systems, there is no attempt to measure any information concerning the frequency spectrum. To make this measurement, the whole of the post-reception signal processing would have to be redesigned (6).

If it is possible to obtain the raw signal from the transducer before it has been processed, then the signal will contain information in the frequency domain which will undoubtedly prove to be useful. Several investigators have been carrying out measurements on tissue using that technique. This involves reception of the signal, digitization

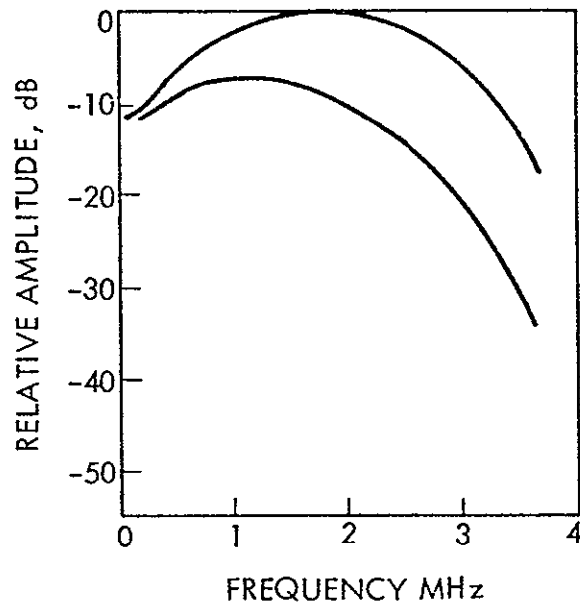


Figure 1. Frequency-amplitude spectrum. Upper curve is that of original pulse. Lower curve shows the spectrum of the pulse after undergoing attenuation of 5 dB MHz^{-1} .

and use of a Fast Fourier Transform method or an analog-spectrum analyzer approach (7, 8, 9).

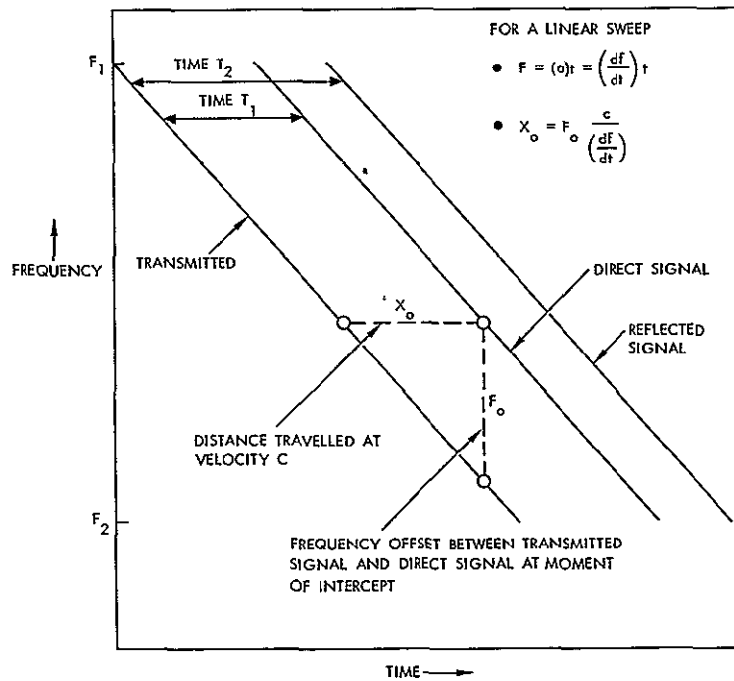
Previous measurements of some tissue properties (velocity, attenuation, etc.) have also been made at a number of discrete frequencies using continuous-wave techniques. These measurements, although useful, have suffered from the problems of reverberation, unwanted echoes, standing waves, etc. There is no way of distinguishing among any one wave in a continuous wave train of single frequency and so it is difficult to select only the direct signal.

III. TIME DELAY SPECTROMETRY

The method used for the measurements on this program is known as Time Delay Spectrometry (TDS). This is a concept invented by Richard C. Heyser (10) which has been used in the diverse fields of audio engineering (11), seismic prospecting, and medical ultrasound. It is a coherent, swept-frequency measurement system which is capable of operating across a wide frequency range. In this case the range is approximately 1 to 10 MHz. The system is able to measure the attenuation of tissue by an insertion method and a curve of attenuation versus frequency can be produced directly.

The basic concept of the TDS system as used in medical imaging and measurements has been published by Heyser and Le Croisette (12). The system described in that paper was considerably upgraded as a major part of the activity of this task. The upgrading is discussed in detail in Section IV. In this section the fundamentals of the method are discussed.

The system uses an ultrasonic transmission repetitively swept in a linear manner from frequency F_1 to F_2 as shown in Fig. 2. At the receiver, the signal has the same format, delayed by the transmission time through the sample. The first signal, received at time T_1 , is normally that via the direct path (line-of-sight) from transmitter to receiver. Any other signal arriving at the receiver, such as the reflected path signal shown in Fig. 3 will arrive at a later time T_2 . A selection of incoming signals is made by a narrow bandpass filter in the equipment in the following manner. The output of the linearly swept ultrasonic generator is heterodyned with a selectable stable frequency source as shown in Fig. 3, producing a replica of the sweep offset in frequency. This subsidiary source may then be set so that the narrow passband of the filter accepts only the signals which arrive via the direct path; all other signals outside of the passband of the filter will be rejected. For example, the reflected path signal, which will incur a greater delay (T_2) on its longer path to the receiver, will be received by the transducer but will produce a heterodyned signal outside



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Figure 2. Time Delay Spectrometry Frequency Sweep.

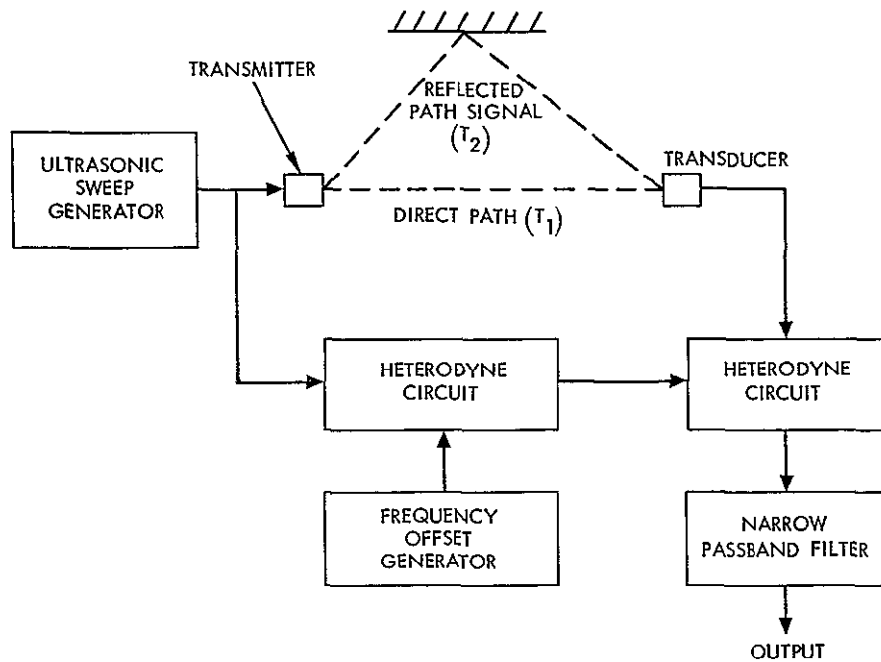


Figure 3. Block Diagram of the System.

of the narrow limits of the filter and will not be accepted. If the frequency of the offset generator is increased, it is possible to selectively accept the reflected path signal and reject the direct transmission. Therefore, by a simple setting of the offset generator frequency, the operator can determine whether he wishes to accept the direct path transmission or reject this and accept only those signals that are delayed by some measurable time (such as the reflected path signal shown in Fig. 3). The minimum path difference that can be resolved (ΔX) is given by

$$\Delta X = \frac{c \ B}{\Delta f / \Delta t}$$

where c is the velocity of propagation, B is the filter bandwidth and $\Delta f / \Delta t$ is the sweep rate. In a typical application, $c = 1500$ m/s, $B = 3000$ Hz, and $\Delta f / \Delta t = 500$ MHz/s. The resolution, ΔX , then becomes 6 mm. Note that these values apply when the frequency dependent information is retained. Considerable improvement in the time and spatial resolution can be obtained by integrating across the spectrum (12).

In the system, a linear frequency-versus-time sweep is generated, so that it is a simple matter to transfer the data between the frequency and time domains. Oscillators with high phase stability are used so that a repetitive output spectrum including both amplitude and phase is fixed by the operator and direct measurements of the characteristics of the soft tissue are obtained as the sweep progresses. This is discussed in more detail in Section IV.

The transmitted signal discussed above can be considered as a predetermined frequency spectrum with the equivalent of a time tag to each frequency component. In this equipment, this consists of a linear frequency sweep with time in which the tag is the moment of occurrence of each frequency. Upon emergence from the tissue, the frequency components with a given time delay are reassembled to yield the frequency spectrum.

This method not only provides the complex spectrum of the signal (with amplitude and phase), but signal components due to longer path lengths, such as those caused by scattering, are effectively suppressed because their spectrum time tags reject them. The signal displayed at this point is the anechoic frequency response of the combined transducers, electronic system and the ultrasonic path through the tissue. A simple calibration procedure through the water bath alone is used to eliminate the constant response of the transducers and electronic apparatus. Thus it is possible to measure the anechoic frequency response, and hence the attenuation, of the ultrasonic energy in its path through the tissue at any point.

The equipment that was available at the beginning of the program is shown in Fig. 4. The center rack contains the basic TDS system and display unit. The larger rack on the right-hand side holds a Panoramic spectrum analyzer. On the left is the automated X-Y scanner. This unit was custom built by Beckman Instruments, Inc. and is an accurate, rugged stepper-controlled system with repeatability of 0.2 mm.

When it is desired to use the system for imaging, the scanner may be set in an automated mode to scan a complete raster covering about a 15 cm x 15 cm area. At the same time, the spot on the screen of the display unit will follow with a raster pattern of the same area scan. The real-time images appear on the Tektronics 603 storage monitor which is the middle CRT unit in the center rack. A gray-scale image on the storage monitor can be obtained in either of two ways. In the first method, the storage capability is switched off and the CRT is used with a polaroid camera. Secondly, a technique of pulse width modulating the beam can be used, which results in a half-tone type image. The resultant image dynamic range is less than that of a monitor without storage but the picture is acceptable.

This equipment, in various forms of development, was used from 1973 to 1976 and proved to be reliable. The electronic design of the unit was based upon that used previously for acoustic testing by co-investigator Richard C. Heyser. A block diagram of the instrumentation is shown in Fig. 5.

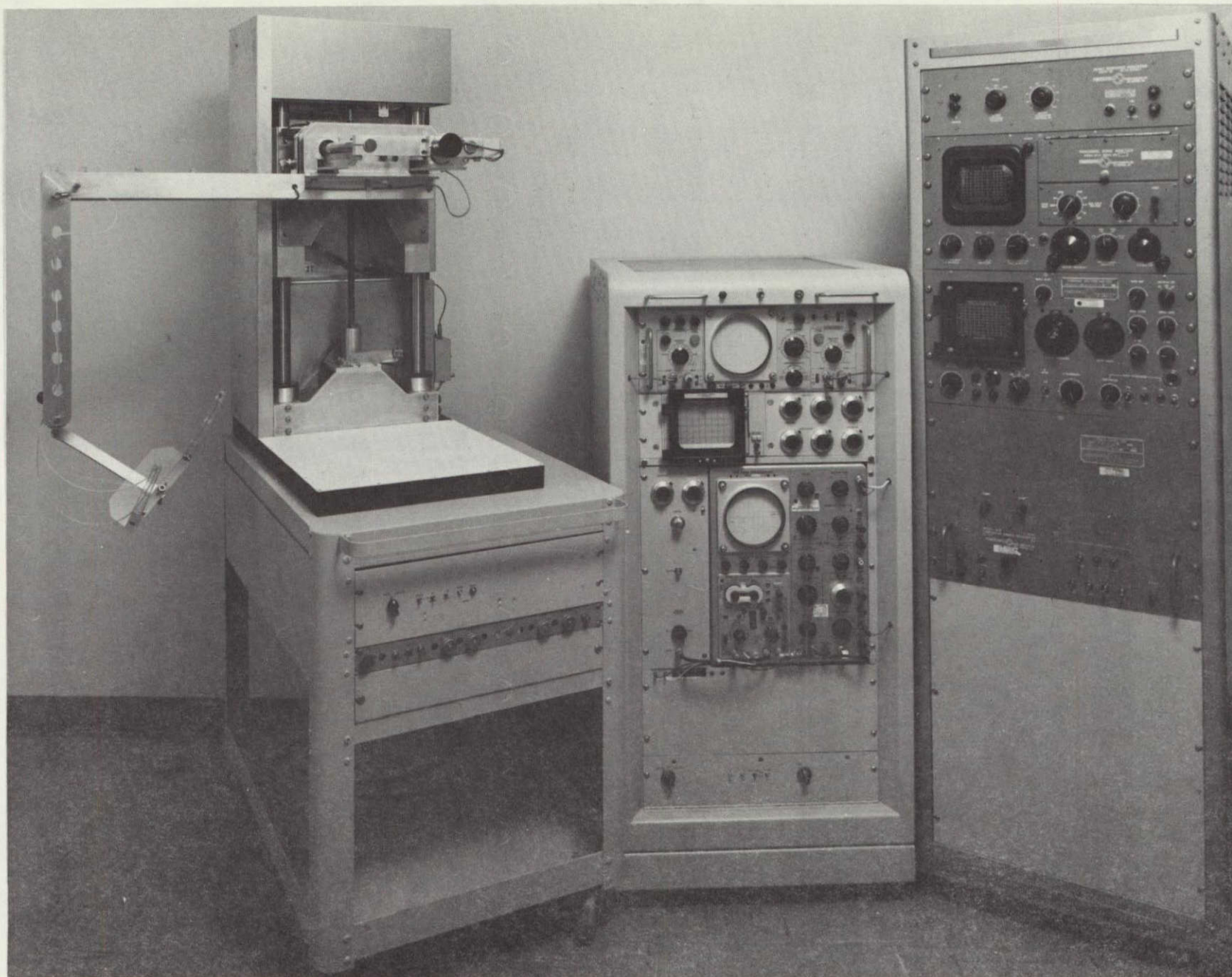


Figure 4. Equipment at the Start of the Program.

A Tektronics spectrum analyzer (plug-in type 1L5) was used in this mode as the primary swept frequency source. This unit was modified to accept a phase coherent frequency reference as well as to provide an intermediate frequency output. The unit as shown swept through the range 2 to 3 MHz. As configured, a raster image and a swept-frequency attenuation curve could be produced by the equipment.

The system using the Tektronics 1L5 spectrum analyzer was used for imaging and for the early data on attenuation spectra over the frequency range of 2 to 3 MHz.

The later spectral data, including all of the attenuation spectra reported during the early phase of this program was taken with a modified Panoramic SPA-3 Spectrum Analyzer. The G-6 tracking generator, designed for use in response measurements with this unit, was modified to produce a sweep that was offset by a selectable amount, namely around 10 kHz. With a sweep rate of 100 MHz/sec, this is just the right amount for the delay through around 15 cm of water.

The system was convenient to operate. The Panoramic SPA-3 provides both a selectable bandwidth filter (usually used at a bandwidth of 500 Hz), a display of the received spectrum in either linear or logarithmic mode, and accurate 500 kHz calibration markers. The G-6 Companion Generator provides a convenient means of obtaining an adjustable offset frequency and, in addition, provides a set of attenuators to produce the calibration curves of the spectra through the water. Although the sweep is not perfectly linear, the constant frequency offset is close enough to being a constant time delay for measurements over a limited frequency range.

In its passage through soft tissue, ultrasound energy is subjected to attenuation, refraction, reflection and diffraction. Attenuation may further be subdivided into absorption and scattering; both phenomena reduce the energy in the directly transmitted beam.

The effects of scattering, refraction, multiple reflection and diffraction combine to reduce the sharpness of an image in a typical B-scan (reflection-mode) picture. The image is similarly blurred in a transmission-mode system. The effects of these various phenomena

provide a major limit to the resolution possible in the conventional pulse-echo system.

The TDS system reduces or eliminates the effects of most phenomena that cause a deviation of the beam from its direct path through the tissue. It has the following characteristics:

- It accepts only those signals which reach the receiver at a given (preset) delay time. If this time equals the transit time between the transmitter and receiver, the system can make anechoic measurements.
- It operates in both the frequency and time domains. Information from one domain may readily be converted to the other.
- It is a coherent processing scheme (not holographic). Signal-to-noise ratio is high and power density requirements are low.
- It can be used to sharpen and make symmetrical the beam from a transducer (12).

IV. EQUIPMENT UPGRADE

It was realized for some time that the original system described in Section III represented a compromise between the capability of the method and the equipment that was available. For this program considerable upgrading of the system was required. The major features in the upgrading were the acquisition of two Dana type 7020 digital frequency synthesizers. These form the basis of the new system shown in Fig. 6.

The two frequency synthesizers are used to generate the necessary source signals. An external logic control subsystem causes both synthesizers to execute a programmed frequency sweep.

The frequency program of both sweeping signals is identical, including the precise phase of each signal at the start of the sweep. The distinction between the two signals is that synthesizer number 2 is programmed to have a preset time delay relative to synthesizer

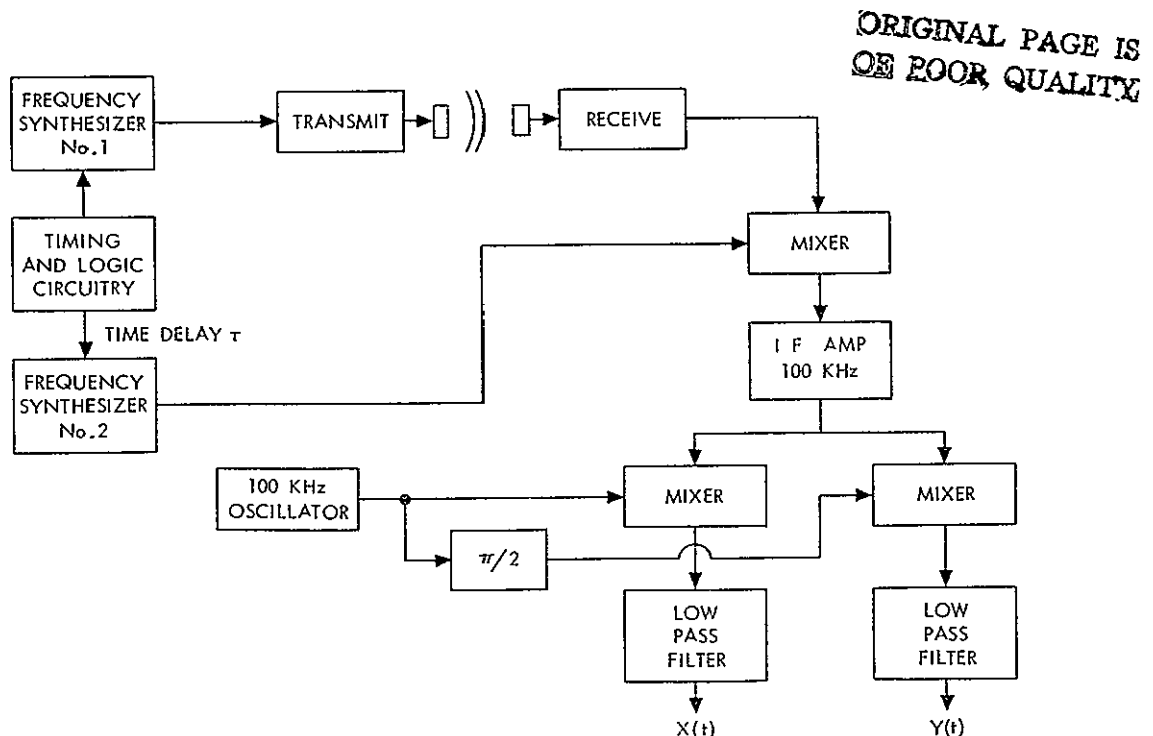


Figure 6. Block Diagram of the New System.

number 1. This time delay is intended to be almost, but not identical to, the transit time delay of ultrasound from transmitting probe through the tissue under test to the receiving probe.

The reason for the slight offset in time delay is to allow a constant heterodyne difference frequency between the ultrasound received signal and synthesizer number 2. If the delay differences were zero, then the ultrasound signal would be heterodyned to zero frequency. This is a perfectly acceptable mode of operation and all the information is contained in this output, but since our interest may be the complete complex signal, which includes phase as well as amplitude, it would be necessary to introduce additional computational complexity to extract this information.

A simpler modality in this case is to constrain the sweep program to a linear frequency sweep and heterodyne to a first intermediate frequency, 100 KHz in this figure. By this means, a sweeping signal which may cover the range from 1 MHz to 10 MHz is converted to a single frequency at 100 KHz. The modulation on this 100 KHz signal, phase modulation and amplitude modulation, conveys the spectral information of the ultrasound signal over the 1-10 MHz range. This is now a time delay spectrometer.

The demodulation of this 100 KHz signal may now proceed by conventional means. In this case the demodulation consists of heterodyning to zero frequency by using two channels which bear a 90 degree phase relationship with each other. The output, after simple low pass filtering to remove unwanted terms, is two signals X and Y. If only the amplitude of the signal is required the two signals X and Y can be squared, summed, and the square root obtained. This value, as a function of frequency can then be displayed on the Panoramic spectrum analyzer as in the simpler system. In the new system, however, there is the capability of obtaining additional information as shown below.

Both X and Y are signals that vary as a function of time. This variation occurs during the time of the receipt of the sweeping signal. The frequency of the signal that is swept has now become equated to time for X and Y.

If full coherence is maintained in the program of the frequency synthesizers and the heterodyning process, then the signals X and Y have a precisely defined mathematical relationship with the frequency spectrum of the ultrasound signal. One of them, say X, will be the true in-phase component of the spectrum, and the other, Y, will be the quadrature component.

The function of the apparatus in Fig. 6 is to provide a means of testing a system in such a way as to isolate all signal components which take a preselected time delay in passage through the system under test, and determine the spectrum of those components.

This spectrum includes both the frequency domain and the time domain, as will now be described. The continuation of the signal processing system is shown in Fig. 7.

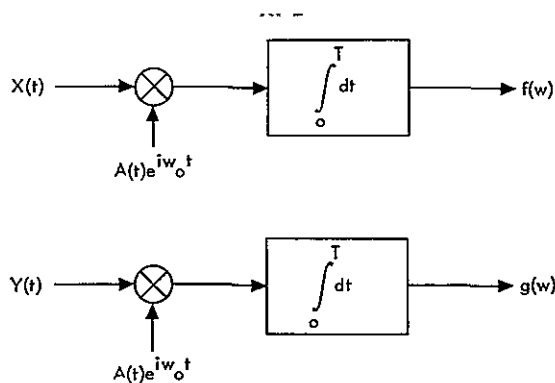
The mathematical interpretation of the signals X and Y is that they are in-phase and quadrature components of the frequency spectrum. If we denote this frequency spectrum with the symbol $F(\omega)$, then,

$$F(\omega) = X(\omega) + i Y(\omega)$$

where

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$$i = \sqrt{-1}$$



$$g(\omega) = \int \frac{f(x)}{\omega - x} dx$$

Figure 7. In-Phase and Quadrature Component Transforms

The instrumentation has converted a frequency metric to a time metric. So the actual signals have the form,

$$F(t) = X(t) + i Y(t)$$

$$(t_1 = \omega_1) \leq t \leq (t_2 = \omega_2)$$

The Fourier transform of this takes the form

$$x + iy = h(\omega) = \int_{t_1}^{t_2} A(t) \cdot F(t) e^{i\omega t} dt$$

where $A(t)$ is an apodizing kernel chosen to yield some specific type of response. The mathematical interpretation of the Fourier transform, as a signal in the actual time domain, is

$$h(t) = f(t) + i g(t)$$

where $f(t)$ is the impulse response of the system under test, and $g(t)$ is the Hilbert transform of the impulse response. The signal $h(t)$ is called the analytic signal associated with the impulse response.

In order to perform the Fourier transform operation, it is only necessary to create the time signal,

$$A(t) e^{i\omega_0 t},$$

multiply this time signal against the signal $F(t)$ and integrate this product over the time interval $(t_2 - t_1)$. The time during which this integral is taken determines the portion of the frequency spectrum that will be used for evaluation of the analytic signal $h(t)$.

In actual practice, the weight kernel $A(t)$ can be used to isolate the portion of the frequency spectrum of interest. In that case the integration proceeds for the entire duration of the received ultrasound signal.

These mathematical expressions are not precise because the 100 KHz intermediate frequency filter bandwidth has selected a range of time delays for the frequency spectrum $F(\omega)$. Again, because of the interchange of time and frequency, this filter shape, as a frequency-dependent property, has been used to perform a time delay selection and apodization. In practice, this bandwidth is made sufficiently broad enough to pass those signals corresponding to the sound path signals of interest while rejecting those lying outside the path delays of interest.

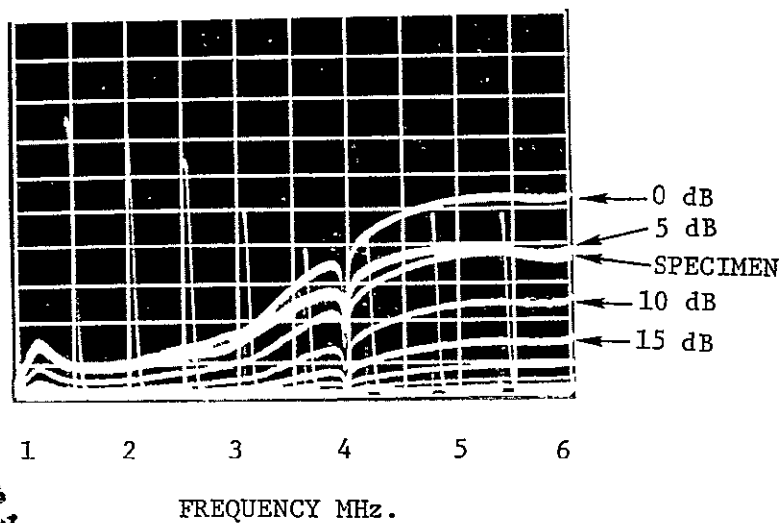
In performing clinical evaluations on tissues in which the possible range of time delays of first path length signals may lie within a window of T_0 seconds, the 100 KHz filter selectivity can be made wide enough to accommodate these delays. By this means, the initial time delay, T , may be set to a value corresponding to a median value of observed tissue delay and no further adjustment need be made thereafter.

The $X(\omega)$ and $Y(\omega)$ signals will therefore contain all the information about the frequency and time delay properties of the tissue for those signal paths lying within a time $\pm(T_0/2)$ of the delay T . If these signals are properly recorded, the detailed analysis may be performed at a later time. Besides the obvious advantage of being able to perform the mathematical analysis at a later time, the analyst has the freedom to choose what type of data to analyze without the need to perform a new measurement on the human subject.

It is repeated that the $X(\omega)$ and $Y(\omega)$ signal analysis has not, in general, been carried out for the tissue analyzed on this program. The instrumentation has the capability to provide the frequency and time delay properties of the tissue if required.

In the earlier system it was only possible to operate the system over about a 4.5 MHz sweep at any one time. This was because the slightly nonlinear sweep of the spectrum analyzer caused the constant frequency offset to represent a varying time delay. Two sweeps are shown in Figure 8. The combination of these two sweeps covers the 1 to 10 MHz range. In this figure the fainter curves are the response of the system with the indicated attenuations. The brighter line below it is the system response when attenuators of 5, 10, 15, 20, etc.

dB are inserted into the line. The stronger trace is the response when a piece of tissue was inserted. From this curve the insertion loss caused by the tissue can be obtained.



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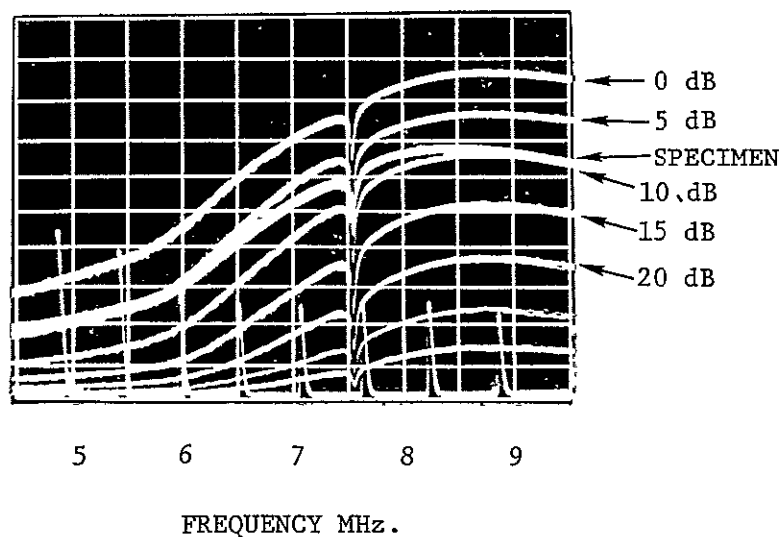


Figure 8. Two Frequency Sweeps from the Original Equipment.

Figure 9 shows the similar output curves for the improved system. It can be seen that the range of 1 to 10 MHz is covered in the one sweep and that the curves are smooth. Curves of this type were taken on all of the tissue measured in about the last year of the program.

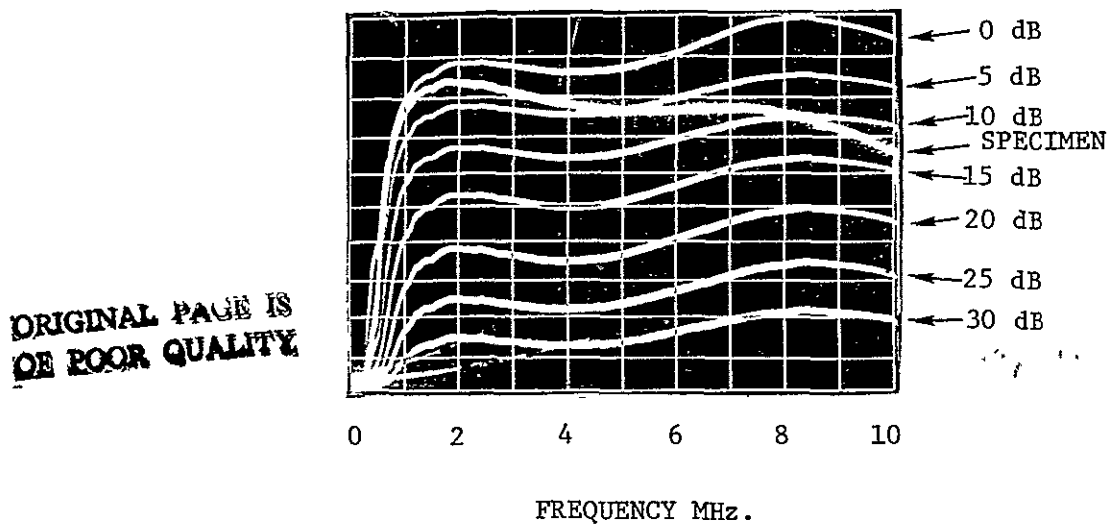


Figure 9. Polaroid print of the output versus frequency of the new system.

V. TRANSDUCERS

At the beginning of the program, a variety of transducers were used as transmitter and receiver. Although unbacked crystals had been used in the past, it is necessary to have a backed heavily damped transducer to obtain a reasonable output over a wide frequency spectrum.

Many tissue studies by other investigators have been implemented using a reasonably broadbanded transducer resonant at the standard diagnostic frequency of 2.25 MHz. For imaging, a transducer resonant at this frequency is good compromise between the loss of resolution that would be experienced at lower frequencies and the reduction in signal because of the higher attenuation of the tissue at higher frequencies. When such a transducer is used for studies over a wide frequency range, however, both the decreasing response of the transducer and the increasing attenuation of the tissue degrade the system signal-to-noise ratio at the higher frequencies. For this reason it is advantageous to consider a transducer resonant at frequencies higher than 2.25 MHz.

For tissue characterization, the primary consideration is the bandwidth over which the response of the transducer is usable, which depends on the resonant frequency of the transducer as well as on its "Q". By definition, $Q = \omega_0 / \Delta\omega$, where ω_0 is the resonant frequency and $\Delta\omega$ is the 3-dB bandwidth. The maximum bandwidth will therefore be obtained if a transducer with the lowest Q and highest practical resonant frequency is selected. The Q depends on the internal damping of ceramic, which is usually low, and on the backing and matching layers of the transducer. The minimum Q that can be obtained for a given type of ceramic does not change rapidly with frequency. Since for a fixed Q the 3-dB bandwidth is proportional to the resonant frequency, this frequency is an important consideration in the selection of a transducer. Rather than selecting a transducer resonant near the lower part of the frequency range of interest it is preferable to use a transducer resonant at the center or upper end of the frequency range. Since the 3-dB bandwidth is greater, the usable bandwidth (which is where the response of the transducer is not down by more than 20 to 40 dB) is also greater.

A transducer of low Q resonant at the upper end of the frequency range of interest, e.g., 10 MHz, has proven to be a good choice for measurements of attenuation in tissues. Not only is the total bandwidth broader, but since the sensitivity of the transducer is greater at the high frequencies, partial compensation is obtained for the higher attenuation of the tissue at those frequencies. By concentrating the output of the transducer at the frequencies that will be most attenuated by the specimen, rather than at the frequency which was chosen to produce good images, a more nearly uniform signal-to-noise ratio at the receiver will be provided.

A choice has to be made between focussed and unfocussed transducers. In the original discussion on the method applied to ultrasound, Heyser and Le Croisette (12) discussed the effect of TDS on sharpening the beam and showed that a considerable reduction in beam width could be obtained by using a wide frequency sweep. This analysis applies only when the frequency sweep is integrated (collapsed) to give a single-value output; when the frequency spectrum information is retained there is much less signal rejection. In this case focussed transducers provide a useful alternative.

The transducers used for much of the measurements in this program were 6 mm diameter, resonant at 10 MHz and heavily damped. These were found to be suitable for use over the whole range. Because of their low sensitivity at the low frequencies, however, a low-pass filter was used. This boosted the output by about 20 dB at about 2 MHz. The 6 dB spot size was 17 mm at 2.5 MHz and the transducers were typically 12 cm apart.

One of the difficulties in making measurements over a wide frequency range is that the spot size varies as a function of frequency since, for an ideal piston, the spot size is determined by the ratio of the diameter to the wavelength. Thus as the frequency increases, the spot size decreases. If there are irregularities in the tissue which are not centered in the beam, the measurement through the frequency range will not be uniform.

Alignment of the transducers is an important factor in the measurements and considerable care is taken in the initial settings to ensure that accurate positioning has been obtained. For most of this program,

the transmitting and the receiving crystal were of the same diameter. This aggravates the alignment problem since the receiver is only intercepting the central portion of the beam and any refraction by the specimen will produce a reduction of signal strength which is independent of the attenuation. This may explain part of the difficulty experienced by this and by other groups in obtaining consistent data in excised canine heart tissue.

Towards the end of this program experiments were conducted using a transmitter and receiver of different sizes, so that the beam even if slightly refracted falls on the receiver. The directivity pattern of the receiver is not determined by its physical diameter, but rather by the area that is actually illuminated. Since this area decreases with increasing frequency, a partial correction is obtained for the change of the directivity of the transmitter with frequency. Furthermore, since the illumination does not suddenly go to zero at the edge, the side lobes are reduced by apodization. Since reciprocity holds, the same results would be obtained by uniformly illuminating a large area of the specimen with a transmitter that is larger than the receiver.

This seems to be a good choice for studying the bulk properties of reasonably uniform specimens. For the study of small pathologies, however, the spot size must be reduced by focusing.

Towards the end of the program a focussed transducer was investigated. The choice for a transducer pair was a 10 MHz, 0.5 inch (1.27 cm) diameter, 2 inch (5.08 cm) focus heavily damped transducer as the transmitter and a 0.25 inch (0.64 cm) diameter, 10 MHz heavily damped unfocused receiver. The transmitter to receiver distance was set at 5 inches (12.7 cm) and the tissue was placed 3.43 inches (8.7 cm) from the transmitter. This is just behind the focal point. A spot size of about 3 mm diameter at 5 MHz was produced. By placing the tissue slightly beyond the focal point critical positioning problems were avoided and diffraction problems were expected to be reduced. This system was not totally successful because the receiving transducer was found to be too small to receive the total energy of the beam under all geometrical conditions. Thus, if the specimen were slightly irregular or not quite normal to the incident energy some fraction

of the beam would not be received by the receiving crystal. This condition obtained even when the crystals were correctly aligned and was most noticeable at high frequencies where the spot size was small.

The last sets of experiments were carried out with the following transducers. Transmitter: 10 MHz, 0.5 inch (1.27 cm) diameter, 3 inch (7.62 cm) focus, heavily damped. Receiver: 10 MHz, 0.5 inch (1.27 cm), unfocused, medium damped. A larger, more heavily damped transducer for the receiver should have been used but was not available. The spot size was increased to about 5 mm diameter at 5 MHz. This combination of transmitter and receiver appears to offer the best compromise with respect to alignment and positioning, spot size, and reducing the effects of tissue inhomogeneity, when the primary concern is studying small areas of pathology.

VI. TISSUE HANDLING

The handling of tissue is the most difficult problem that the investigators faced in the program. Tissue handling requires a great deal of time, is critical to the success of the measurements, requires considerable experience, is usually treated as being a trivial problem, is greatly underrated, and is messy. It is difficult to transfer the information gained in handling tissue properly except by working in the laboratory.

Soft tissue is not homogeneous, and the changes in thickness and the surface roughness are of the same order as the wavelength of ultrasound used in these experiments (0.15 to 1.5 mm). Although the use of TDS reduces the effects of multipath interference and certainly allows the phenomenon of interference to be readily identified, soft tissue measurements cannot be made indiscriminately. Variations in effective path length cause multipath interference effects which are seen as cusping in the frequency spectrum. At certain frequencies the signals reaching the receiver from paths of differing length may partially cancel and the total signal is reduced. As the frequency is increased the phase difference of the various paths will change and at some frequency the various signals from the differing paths will add to give a maximum. Thus as the frequency is swept through a wide range, as in this equipment, a pronounced cusping may occur. The effect must be taken into account in any ultrasound measuring system even though it is not readily identified in some systems.

In the precision measurements of the frequency characteristics of attenuation which were carried out, multipath interference can be observed directly as cusping in the frequency domain as displayed on the CRT screen. In the imaging mode, the use of Time Delay Spectrometry will remove much of the effects of multipath phenomena because the system accepts only those signals with a constant time delay. When used to determine the frequency variation of attenuation, however, where Time Delay Spectrometry is not used to any substantial extent, frequency cusping can still occur. Furthermore, when a small spot size is used the effects become worse because the topology of the surface of tissue appears to indicate that the fractional variation in

thickness is larger over a small area (say 3 mm diameter) than a larger one (6 mm diameter).

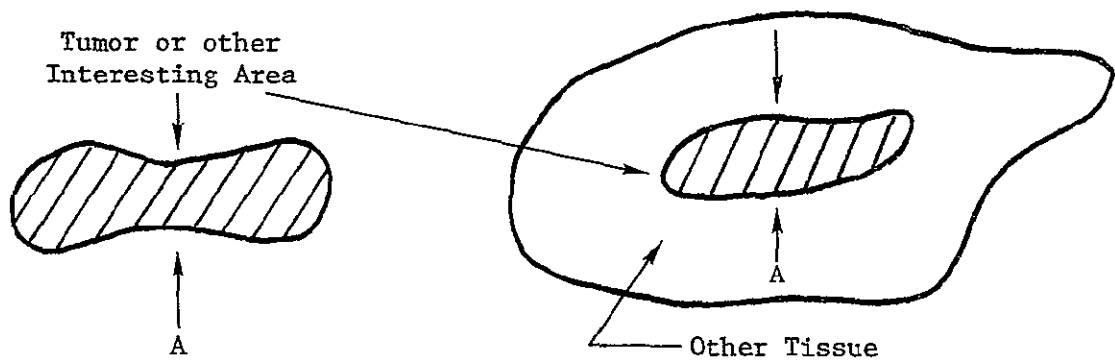
In addition to this problem of multipath interference, the general problems of tissue handling and measurement occupied the attention of this research group over the whole of the program. Measurements of soft tissue are difficult because tissue is not homogeneous and does not remain constant with time after it has been excised. Values of attenuation, for example, reported by many investigators show standard deviations of about 0.3 of the average values.

Whenever practical, five locations in the specimen were studied that were normal, free from major vessels or other intrusions, and are at least 1.5 cm from the edge of the specimen and 1 cm from the other locations studied. After eliminating data that was unusual or suspect, the data from these locations was averaged. Typically data is reported at every 0.5 MHz, which is more than adequate to represent the frequency dependence of any tissue specimen we have seen in either our laboratory or in the literature.

In this program an emphasis was placed on the measurement of homogeneous tissues and on some pathological areas that were of sufficient size for the accurate determination of their ultrasonic characteristics. To improve communication with the medical personnel, the drawing shown in Figure 10 was made which indicates the tissue sizes on which reliable data can be obtained.

Early in the program it was observed that fixing altered the mechanical properties of the tissue. In a typical fresh specimen of breast tissue, for example, the normal tissue is very flexible resembling a fresh piece of meat. The surfaces, although irregular, are relatively smooth. A tumor is usually conspicuously firmer and easily palpated. After fixation, the tumor is still firm with unchanged consistency. Normal tissue, however, was observed to harden and lose its integrity. This consistency can best be described as that of a "charred rubber toy". In the case of liver and kidney tissue, however, formalin fixing has the effect of producing hardness equivalent to an automobile tire.

It is possible that the manner of handling the tissue and the rate at which the physiological saline is replaced by formalin may determine how much the mechanical properties, namely the spatial variation of the density and elasticity, determine the measured ultrasonic properties. These mechanical properties are far more susceptible to the effects of formalin fixing than are the radiological properties (which are determined primarily by atomic number density) or visual appearance. A number of ultrasound measurements have been made by other investigators on fixed tissue. It is apparent from the measurements discussed in Section VIII that there can be a substantial difference in ultrasonic properties between fresh and fixed tissue.



"A" is the smallest dimension of the lesion to be identified in the plane of viewing.

IDEAL:	A is 17 mm or greater
ACCEPTABLE:	A is between 7 and 17 mm
IMPOSSIBLE:	A is less than 7 mm

Thickness in the direction of the paper not critical.

Figure 10. Required Specimen Dimensions

VII. DATA HANDLING

In the first year of the program the data were measured over two overlapping 4.5 MHz sweeps. The following measurement procedure was used in the two-scan method. The offset oscillator was first tuned for the maximum signal through the water path and the bag containing the solution (but not the specimen). The overall response was obtained and the system calibrated by taking multiple exposures of the spectrum with 0, 5, 10, 15, 20, 25 and 30 dB of attenuation switched into the system. These curves, together with the 500 MHz frequency calibration markers provided with the Panoramic unit, provided calibration on every photograph.

The scanner was used to move the probes to the desired location on the specimen, which was determined visually. Location of the specimen midway between the transducers was also verified visually. The spectrum was observed for evidence of multipath propagation, namely scalloping or sharp dips in the spectrum. Since the display is logarithmic, extreme multipath cancellation was evidenced by a dip in the spectrum which was cusp shaped, rather than sinusoidal. The scanner was used to move the transducers about 3 mm to either side of the desired location in both the X and Y direction while the displayed spectrum was observed for evidence of multipath interference. If the location selected seemed free of multipath effects over this portion of the spectrum, a picture of the spectrum through the specimen was taken. If the location was not free from multipath effects another location, at least 6 mm away, was used.

The center frequency of the analyzer was then changed and a picture of the other half of the spectrum taken. The offset did not normally require adjustment for a change in the center frequency. The transducers were then moved away from the specimen and a set of frequency markers and the calibration spectra were also recorded. A principal aim of this method was to fix the transducers in one position for both the high and low frequency scans so that relocation was not necessary from one scan to the next while calibration was made.

A typical pair of photographs has been shown previously in Figure 8. These two photographs constitute the data on a specimen. Data reduction in these cases was straightforward and did not depend on the linearity of the display. Since data were usually reported only at 500 KHz intervals, the calibration markers provide an exact determination of the frequency. The attenuation of the specimen was determined by visual interpolation between the calibration curves which are separated by 5 dB from each other. The two photographs overlap in the frequency range 4.5 to 5.5 MHz. This provides another check on the reproducibility as these should agree to less than 1 dB. Disagreement by much more than this amount suggested that there is a problem in the measurement.

Each specimen was measured at four or five points. This was a compromise between sampling enough locations to insure that the measurements were representative and reducing experiment time to a minimum. Since tissue is known to deteriorate rapidly at 37°C, it is important that the experiment time be kept as short as possible.

These measured values of tissue attenuation exhibit considerable variability. At this stage in the experiment it was considered that little was to be gained by applying statistical analysis on the four or five readings taken although it was recognized that a mean and variance should be made on readings from a higher number of points.

After the equipment was upgraded there was a reevaluation of the statistical handling of the results. A local Hewlett-Packard 2116 minicomputer was programmed to perform an averaging function. The spectral data was fed into the system after being read from the Polaroid prints and the average and standard deviation was printed in graphical form by a line printer to the nearest 0.5 dB/cm. For much of the data which was taken on this program, and for almost all of the later work, measurements at nine locations were made on the tissue and the 5 to 9 most consistent spectra were averaged.

VIII. TISSUE MEASUREMENTS

A. Fixed and Fresh Animal Tissue

Measurements were made to determine the effects of aging and fixing on tissue. The reason for investigating tissue under these conditions was that many previous measurements have been reported on fixed tissue and on tissue that was several days post mortem. These measurements allow a comparison with fresh tissue to be made. Experiments were conducted over the frequency range 1.5 to 9.5 MHz. Two Aerotech Alpha transducers were used. The 10 MHz, 0.63 cm diameter (0.25 inches) unfocussed transducers were selected so that the resonant frequency was just above the range of interest.

Measurements of attenuation versus frequency were made on pancreas, kidney, fat and liver specimens of hog tissue. The measurements were taken under controlled conditions of temperature and formalin fixing to determine the effects of aging and fixing on the tissue. Specimens of tissue from hogs were obtained as soon after slaughter as possible and were studied within 2 to 5 hours of slaughter. The tissue type and time sequence of the measurements are shown in Figure 11. All specimens were heat sealed in a plastic bag containing either 0.9% saline or formaldehyde diluted 10:1 with water (i.e., approximately 4%). The liver specimens were sliced to approximately 15 mm thickness; the kidney and pancreas specimens were studied intact. The backfat specimen was left in the form of a slab as it was stripped from the carcass. The thickness of all of the specimens was calipered at the locations studied. Fat is normally removed one day after slaughter which accounts for the one-day delay shown in Figure 11.

Figures 12 through 19 show the measured attenuation versus frequency for the hog tissue at 37°C. Four or five locations of each specimen were studied. Obvious ducts, vessels, and tapered edges were avoided. In the case of the kidney, measurements were not made in the central portion, which contains the large vessels and the renal pelvis. All of the kidney measurements were made in the region of the pyramids, and so include both cortical and medullary matter. The locations

studied on any given specimen can be identified by the shape of the symbol used on Figures 12 through 15. That is, the circle, square, or triangle represents the same visible location on the specimen when studied on the day of slaughter, five days later, and after fixing. Care was taken to avoid multipath effects by visual inspection of the area of the specimen and by observing the spectrum analyzer for obvious signs of multipath interference. Since no fine structure was observed in the attenuation versus frequency curves, the data are reported at 0.5 MHz intervals.

Each specimen was measured at four or five points. As discussed in Section VII this was a compromise between sampling enough locations to insure that the measurements are representative and reducing experiment time to a minimum. Since tissue is known to deteriorate rapidly at 37°C, it is important that the experiment time be kept as short as possible.

These measured values of tissue attenuation exhibit considerable variability. This is consistent with the experience of other investigators. Accordingly, the averaged or summarized data is presented in the form of band diagrams in Figures 16 through 19. These bands were selected to follow the data with no more than 10% of the points falling outside of the band.

Figure 12 shows the plot of attenuation versus frequency for hog pancreas under four conditions; (a) six hours post-mortem (fresh), (b) five days post-mortem (fresh), (c) fixed five hours post-mortem, and (d) fixed five days post-mortem. Storage of the fresh tissue at 5°C results in a decreased attenuation, particularly at the higher frequencies. These data do not seem conclusive, however, since Figure 12(b) shows a bimodal distribution of readings. The organ lacks rigidity and so accurate placement and replacement of the transducers on these specimens is very difficult. In addition, the hog pancreas contains lobules of glandular tissue on the order of 1 cm, interspersed with fat. It is therefore considered that the wide spread in data can be accounted for by the lack of rigidity and the inhomogeneity of the

specimen. Figure 16 shows the bands of attenuation versus frequency for the fresh specimens under two conditions; six hours and five days post-mortem.

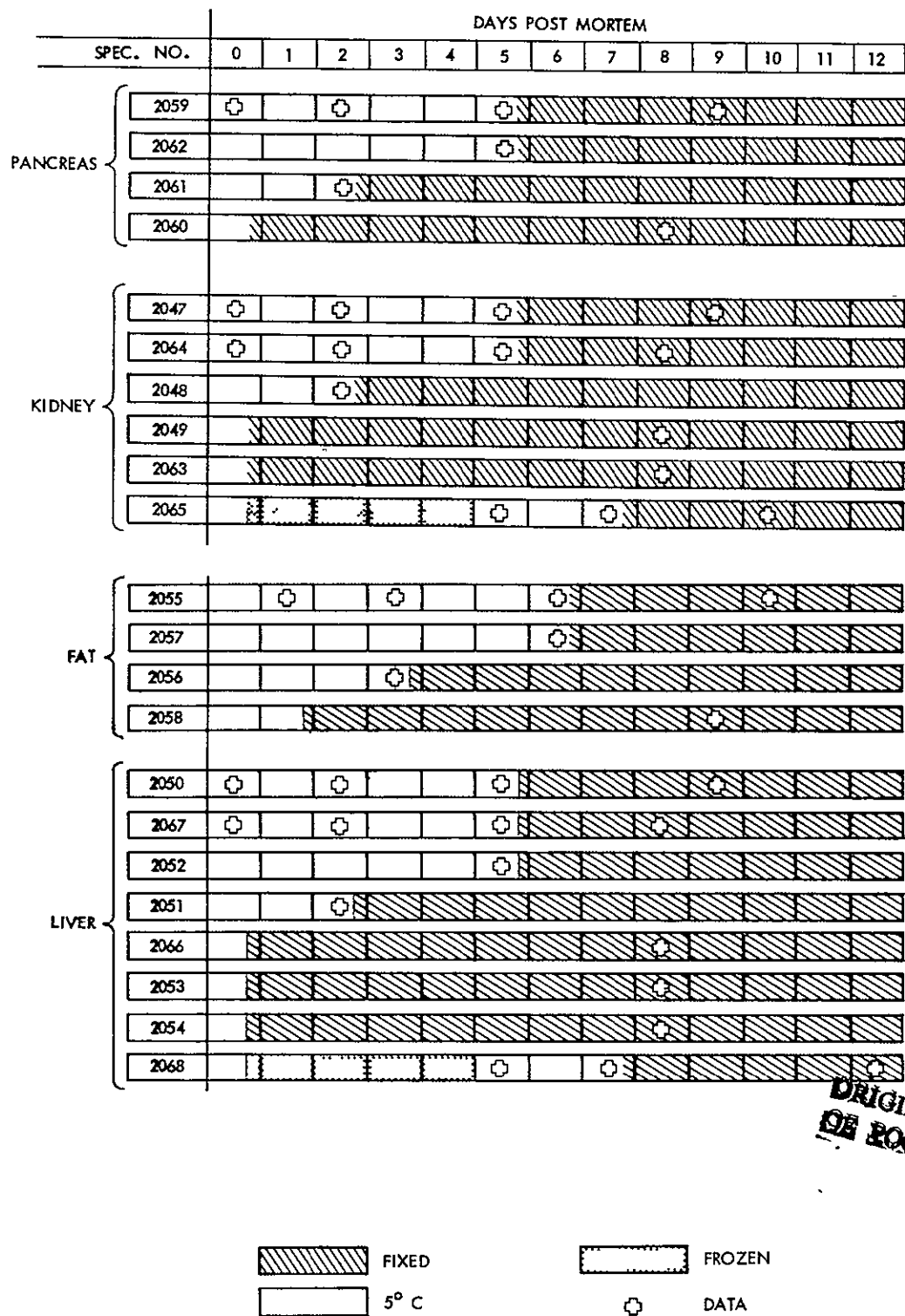
The measurements on fresh and fixed kidney are shown in Figure 13 and the corresponding bands of attenuation are given in Figure 17. For the fresh specimens, storage of the tissue at 5°C for five days has resulted in a decrease in attenuation, especially at the higher frequencies. Measurements taken 48 hours post-mortem (not reported here) lie between the two values. This decrease is just sufficient to separate the band curves. The attenuation of fixed tissue is above that of the tissue just post-mortem.

Figures 14 and 18 made on hog fat show that there is little effect of aging on the attenuation characteristics. Little significance can be placed on the differences at low frequencies shown in Figure 18 since the attenuation is only of the order of the uncertainties in the measurements. Fixing the specimens gives a slightly higher attenuation. There is considerable difference between this fat and typical fat found in human studies so that these data should be applied with caution. Hog fat is white and of a uniform texture whereas human fat is yellow and has a lobular structure with connective tissue interspersed.

Figures 15 and 19 show the data for hog liver. Here the storage of a fresh specimen results in a lower attenuation over a five-day period. The fixed specimens show increased attenuation. The data bands are fairly narrow probably because of the homogeneity of the tissue at the resolution level studied.

These tissue specimens were stored at 5°C and heated to the measurement temperature of 37°C over about a one-hour period. Following this procedure, each specimen was returned to the refrigerator for storage until the next measurement was made or until the specimen was fixed. For comparison, some specimens were held undisturbed at 5°C until a single measurement was taken. No significant difference in attenuation could be seen between the two groups.

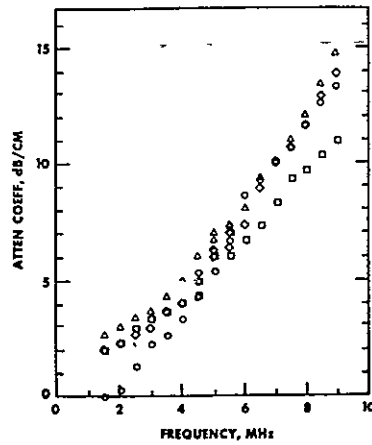
The accuracy of these measurements which were made before the final upgrade of the equipment relies upon the internal sweep linearity of



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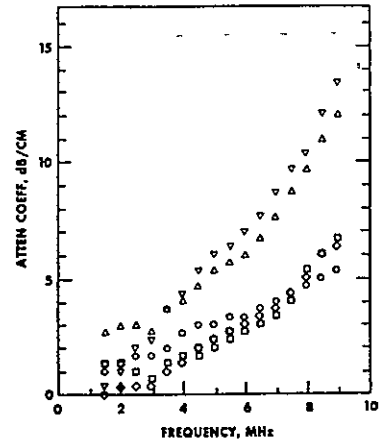
Figure 11. Time Sequence of Measurements on Hog Tissue.

SPEC 2059R HOG PANCREAS 37°C
6 HOURS P.M.
4 LOCATIONS



(a)

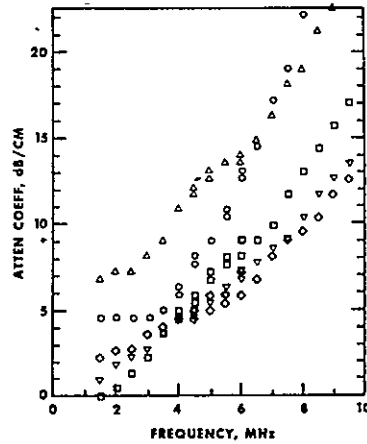
SPEC 2059R HOG PANCREAS 37°C
5 DAYS P.M.
5 LOCATIONS



(b)

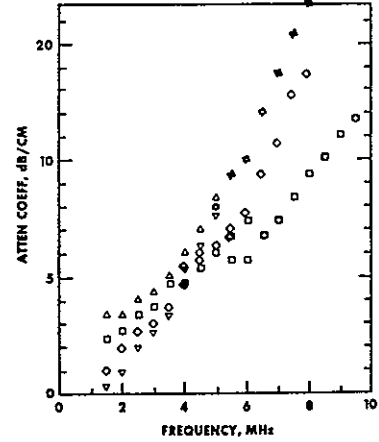
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SPEC 2060X HOG PANCREAS 37°C
FIXED 5 HOURS P.M.
5 LOCATIONS



(c)

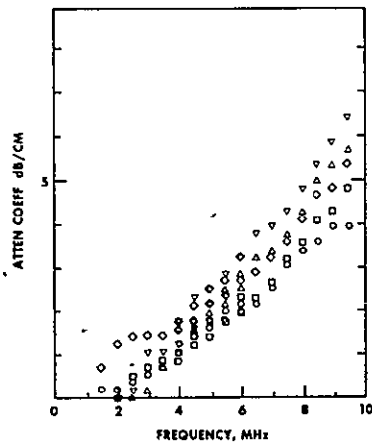
SPEC 2059X HOG PANCREAS 37°C
FIXED 5 DAYS P.M.
4 LOCATIONS



(d)

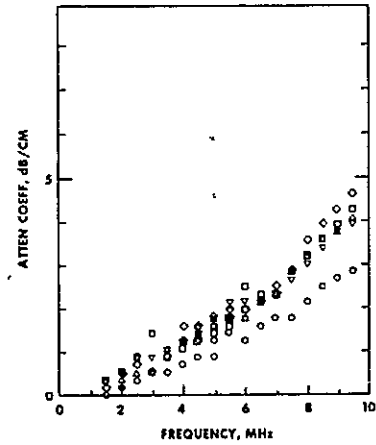
Figure 12. Attenuation versus Frequency Measurements for Hog Pancreas: (a) 6 hours post-mortem (fresh), (b) 5 days post-mortem (fresh), (c) 5 hours post-mortem (fixed), (d) 5 days post-mortem (fixed).

SPEC 2064R HOG KIDNEY 37°C
 ~3 HOURS P M
 5 LOCATIONS



(a)

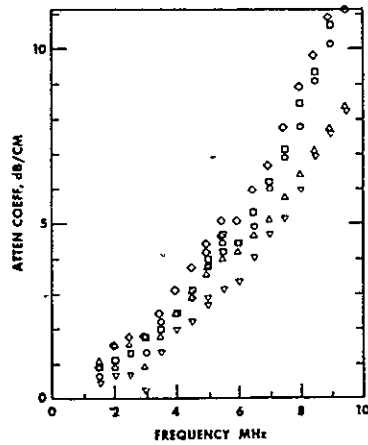
SPEC 2064R HOG KIDNEY 37°C
 5 DAYS P M
 5 LOCATIONS



(b)

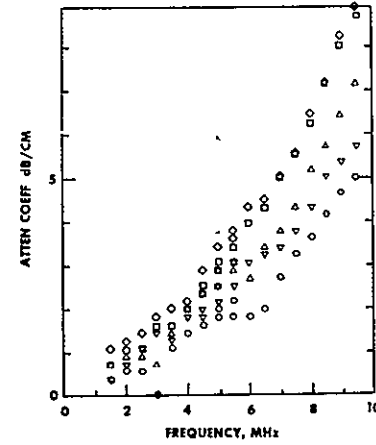
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SPEC 2063X HOG KIDNEY 37°C
 FIXED 4 HOURS P M
 5 LOCATIONS



(c)

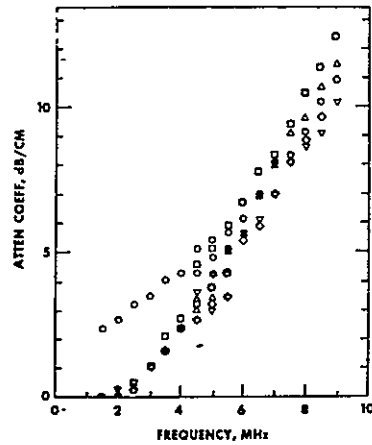
SPEC 2064X HOG KIDNEY 37°C
 FIXED 5 DAYS P M
 5 LOCATIONS



(d)

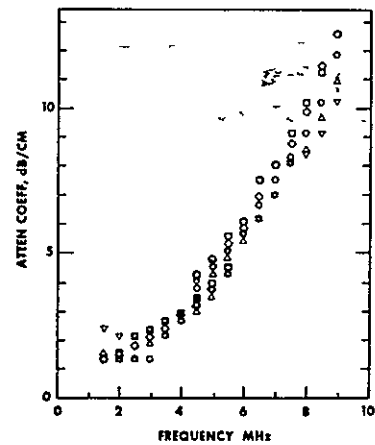
Figure 13. Attenuation versus Frequency Measurements for Hog Kidney: (a) 3 hours post-mortem (fresh), (b) 5 days post-mortem (fresh), (c) 4 hours post-mortem (fixed), (d) 5 days post-mortem (fixed).

SPEC 2055R HOG BACKFAT 37°C
1 DAY P.M
5 LOCATIONS



(a)

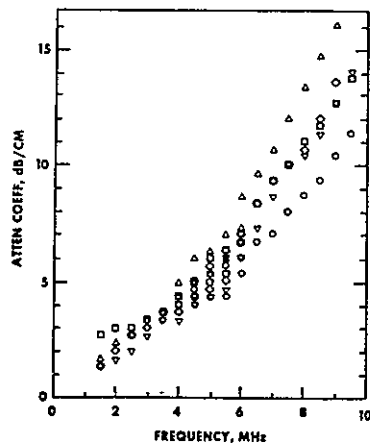
SPEC 2055R HOG BACKFAT 37°C
6 DAYS P.M
5 LOCATIONS



(b)

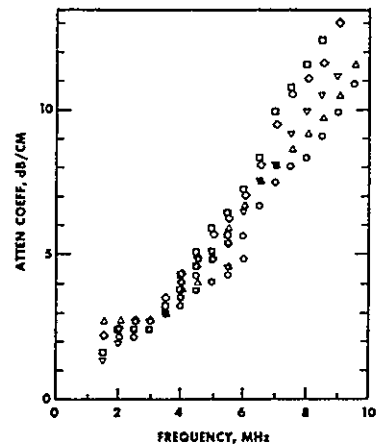
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SPEC 2058X HOG BACKFAT 37°C
FIXED 1 DAY P.M
5 LOCATIONS



(c)

SPEC 2055X HOG BACKFAT 37°C
FIXED 6 DAYS P.M
5 LOCATIONS

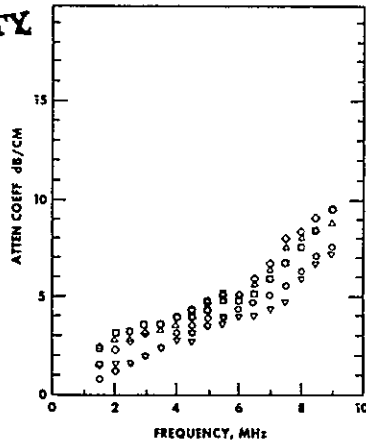


(d)

Figure 14. Attenuation versus Frequency Measurements for Hog Backfat:
(a) 1 day post-mortem (fresh), (b) 6 days post-mortem (fresh),
(c) 1 day post-mortem (fixed), (d) 6 days post-mortem (fixed).

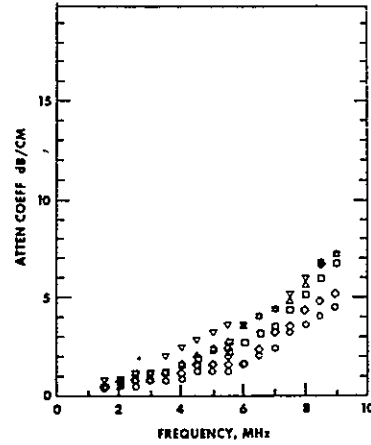
ORIGINAL PAGE IS
OF POOR QUALITY

SPEC 2050R HOG LIVER 37°C
5 HOURS P M
5 LOCATIONS



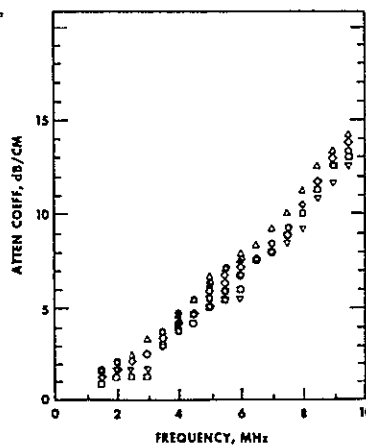
(a)

SPEC 2050R HOG LIVER 37°C
5 DAYS P M
5 LOCATIONS



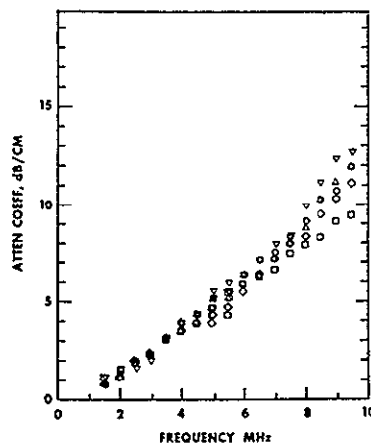
(b)

SPEC 2053X HOG LIVER 37°C
FIXED 5 HOURS P M
5 LOCATIONS



(c)

SPEC 2050X HOG LIVER 37°C
FIXED 5 DAYS P M
5 LOCATIONS



(d)

Figure 15. Attenuation versus Frequency Measurements for Hog Liver:
(a) 5 hours post-mortem (fresh), (b) 5 days post-mortem (fresh), (c) 5 hours post-mortem (fixed), (d) 5 days post-mortem (fixed).

SPEC 2059R HOG PANCREAS 37°C
4-5 LOCATIONS

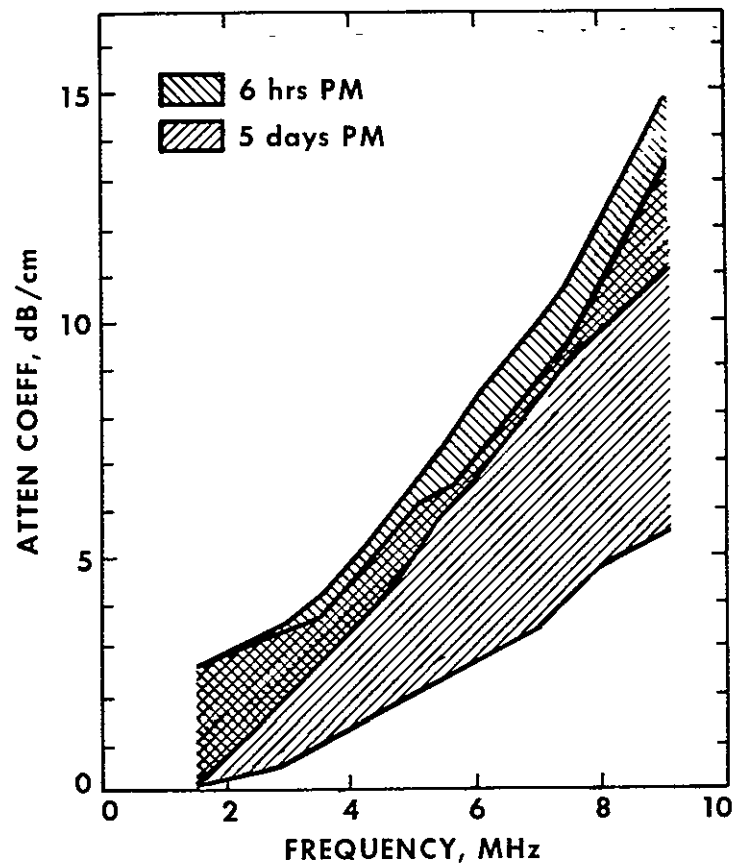


Figure 16. Band Diagram of Attenuation versus Frequency for Hog Pancreas.

SPEC 2064R HOG KIDNEY 37°C
5 LOCATIONS

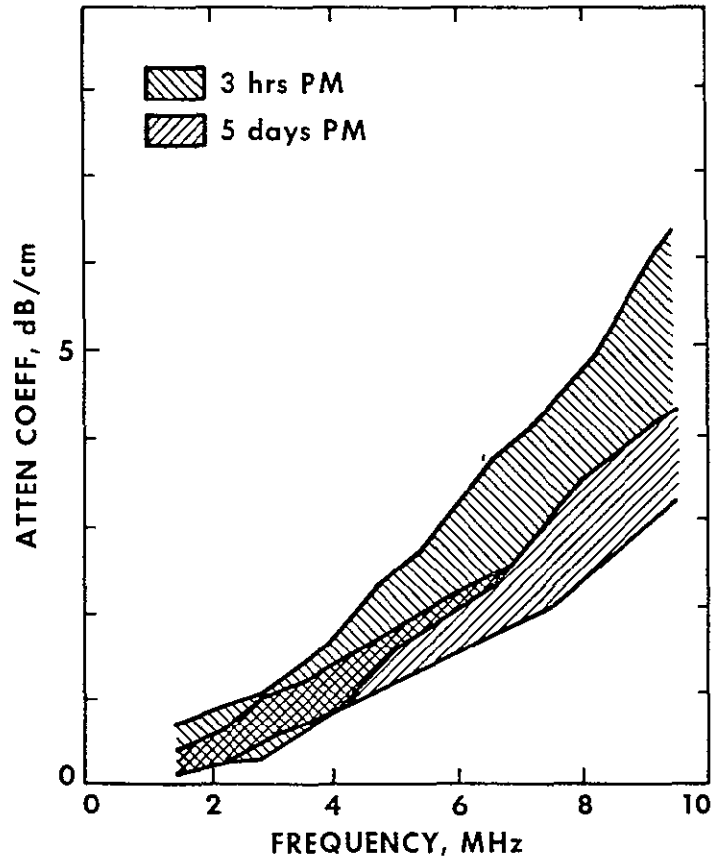


Figure 17. Band Diagram of Attenuation versus Frequency for Hog Pancreas.

SPEC 2055R HOG BACKFAT 37°C
5 LOCATIONS

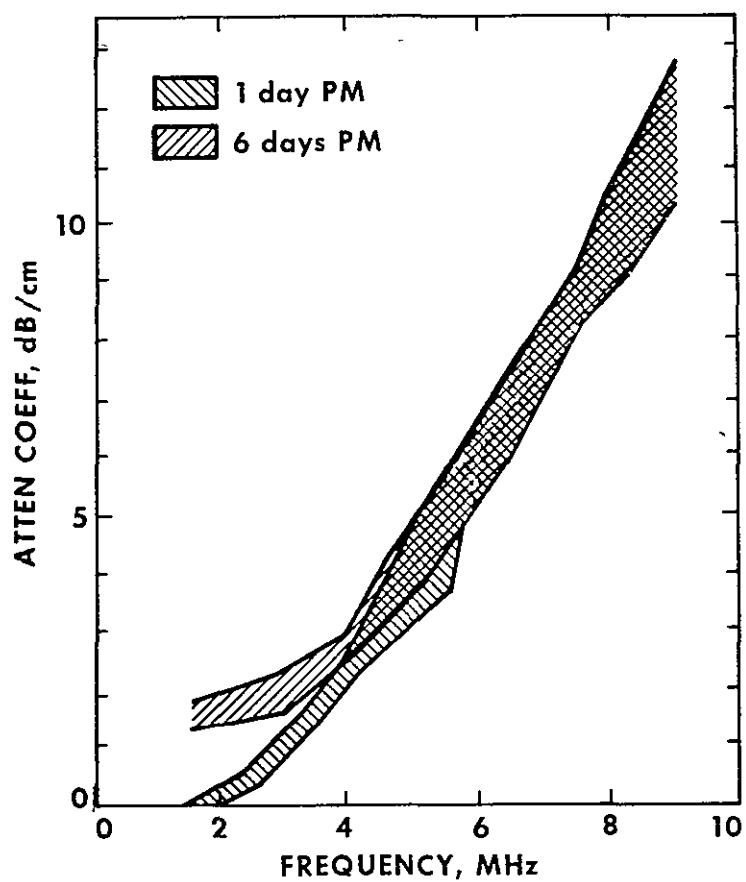


Figure 18. Band Diagram of Attenuation versus Frequency for Hog Backfat.

SPEC 2050R HOG LIVER 37°C
5 LOCATIONS

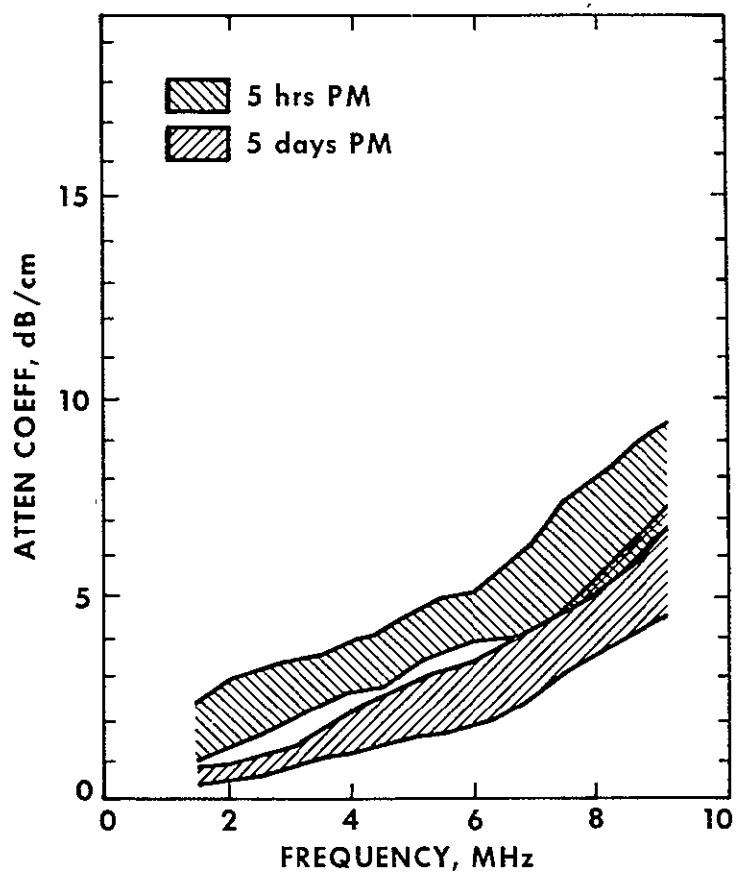


Figure 19. Band Diagram of Attenuation versus Frequency for Hog Liver.

the spectrum analyzer to provide a constant time delay across the frequency band matching the constant transit time of the sound energy through the specimen. Slight non-linearities in the sweep were observed to give an error as high as 1 dB in the measured attenuation. Some indication of this error may be seen in the region between 4.5 and 5.5 MHz. In practice, two sets of data were taken; the lower half extended from 1.5 to 5.5 MHz and the upper part from 4.5 to 9.5 MHz. Small errors in the overlapping region are indicated by two values being plotted with the same symbol. In many cases identical values were obtained or the error was small.

B. Variation of Attenuation with Temperature

Another series of measurements over the frequency range 1.5 to 10 MHz was made to determine the variation of ultrasonic attenuation as a function of temperature for porcine liver, backfat, and kidney. A major reason for performing these experiments is that many of the early measurements reported by other investigators were made at room temperature, while in some cases the temperature was not even recorded. Temperature is expected to have an effect on the attenuation of the tissue, especially if an appreciable portion of the attenuation is due to macromolecular absorption, as some investigators have suggested (13).

The temperature dependence of the ultrasonic properties of excised tissues is needed for several other reasons. The temperature dependence must be known in order to relate reportings at other temperatures to the likely values at body temperature. The temperature dependence must be known at least approximately to determine the tolerance to which the temperature must be maintained for accurate reporting. If relaxation mechanisms are to be elucidated, the temperature dependence as well as the frequency dependence must be determined. Ideally, conjugate properties, such as attenuation and velocity, should be determined in order that dispersion relations can be applied. Even a crude survey of the temperature and frequency dependence may confirm a relaxation mechanism or provide strong support for the dominance of scattering or other phenomena.

This study was carried out mainly with hog organs since they are large mammalian organs that can readily be obtained fresh. The results shown here on these organs are expected to indicate the general trend of mammalian tissues, although the exact values may differ among species.

Internal hog organs were obtained soon after slaughter and were studied a few hours post mortem. The hog backfat was obtained the day after slaughter, which is when it was stripped from the carcass. The earlier study shows that, at least after the first four hours, the attenuation changes little over the course of a day, so the attenuation data can be considered representative of that of the living animal.

Data were taken at three temperatures to demonstrate the general temperature dependence of attenuation. This is sufficient to place definite limits on what models may be applied and to identify what parameters would have to be carefully controlled in more extensive future studies. The three temperatures chosen were body temperature, room temperature, and a few degrees above the freezing point of water. The first temperature was chosen because it is the most representative of the natural state of tissue. The second temperature is the most convenient for pilot data and the one often used in many of the early studies. The last is the lowest temperature at which tissue can be studied in a representative (non-frozen) state and is of interest if enzyme and bacterial action is to be retarded. The proposed temperature range is the largest over which specimens can be studied in a representative state since autolysis is hastened at temperatures much above body temperature.

The specimens were heat-sealed in a standard specimen bag containing 0.9% saline. The bag was suspended vertically between the transducers in a water bath. Care was taken to be sure no air clung to the specimen bag or to the specimen. Data were recorded as before on Polaroid film over the frequency range of 1.5 to 9.9 MHz. Individual points at 0.5 MHz intervals were selected to form the data record. The upgraded equipment was used for these measurements. The synthesizers were swept from 0 to 9.9 MHz at the rate of 500 MHz/second. This rate, together with a total bandwidth of 3,000 Hz at 3 dB down at the receiver output provides

adequate time resolution to eliminate reflections from the sides of the tank, while providing frequency resolution to distinguish the response at frequencies separated by 500 KHz.

The transducers used were Aerotech Alpha 0.25" (6 mm) diameter, unfocussed, 10 MHz highly damped transducers. When used in an otherwise flat transmission system they give about 30 dB difference in response between the resonant frequency of 10 MHz and a lower frequency of 2 MHz. The response of the whole system using these transducers was considerably flattened by a low-pass filter incorporated before the transmitting transducer.

The transducers were 12 cm apart and the sample was placed midway between them. These are plane, circular, unfocussed transducers and the spot size of any such simple transducer is frequency dependent. The spot diameter at 6 dB below maximum response is calculated to be 6.6 mm at 8 MHz, 8.1 mm at 5 MHz, 10.7 mm at 3 MHz, and 14.1 mm at 2 MHz.

To minimize specimen deterioration, data was acquired as rapidly as possible and the specimens were kept in a refrigerator (approximately 5°C) when not being studied. The attenuation values were first measured at 37°C and these were compared with measurements made at 37°C the next day to verify that the specimen had not deteriorated significantly during the handling.

After the specimens were placed in the water bath in their sealed plastic bags they were allowed to equilibrate for at least 20 minutes before measurements commenced. The alignment of the transducer probes was verified and the setting of the TDS delays were changed whenever the temperature was altered. The temperature was maintained to $\pm 1^\circ\text{C}$. As before, the system response was determined by obtaining calibration spectra through the water path, with 0, 5, 10 . . . 35 and 40 dB switched into the signal path. These calibration spectra were recorded from an oscilloscope display by multiple exposure on to a single Polaroid photograph.

A location was then selected on the specimen for the attenuation measurement. Nine locations were studied, approximately 5 to 10 mm

apart. Since the average specimen characteristics were desired, rather than localized pathology information, no attempt was made to record the exact location on the specimen. In the interest of speed and economy, data from three locations were recorded on the same Polaroid photograph.

As before, an attempt was made to verify the absence of multipath effects which cause phase cancellation. Since the new system displays nearly 10 MHz in one real-time display, it is easy to spot dips in the spectrum which are characteristic of multipath interference. As an additional test the scanner mechanism was used to move the transducers approximately 2 mm to either side of the selected spot on the specimen in both the horizontal and the vertical direction, while observing the displayed spectral response. If multipath interference was evident at one specimen location, another position was chosen.

Each specimen was measured at nine locations. This permitted a meaningful statistical average to be calculated. A spectrum was rejected after it was plotted if it was judged to be quite unrepresentative of the tissue because of the presence of pathology or discontinuities.

The total reflection loss at the surface of the specimen and the bag is estimated to be less than 1 dB and so no correction for the loss has been applied. A separate series of measurements was made to confirm that losses by reflection and attenuation because of the presence of the bag were small.

As an additional check, the attenuation of the backfat specimen was measured both with the specimen intact and on the two pieces after it was sliced in two. These readings were in agreement. The specimen thickness was measured with mechanical calipers, taking care not to indent the surface of the specimen and to measure several locations to determine the representative thickness.

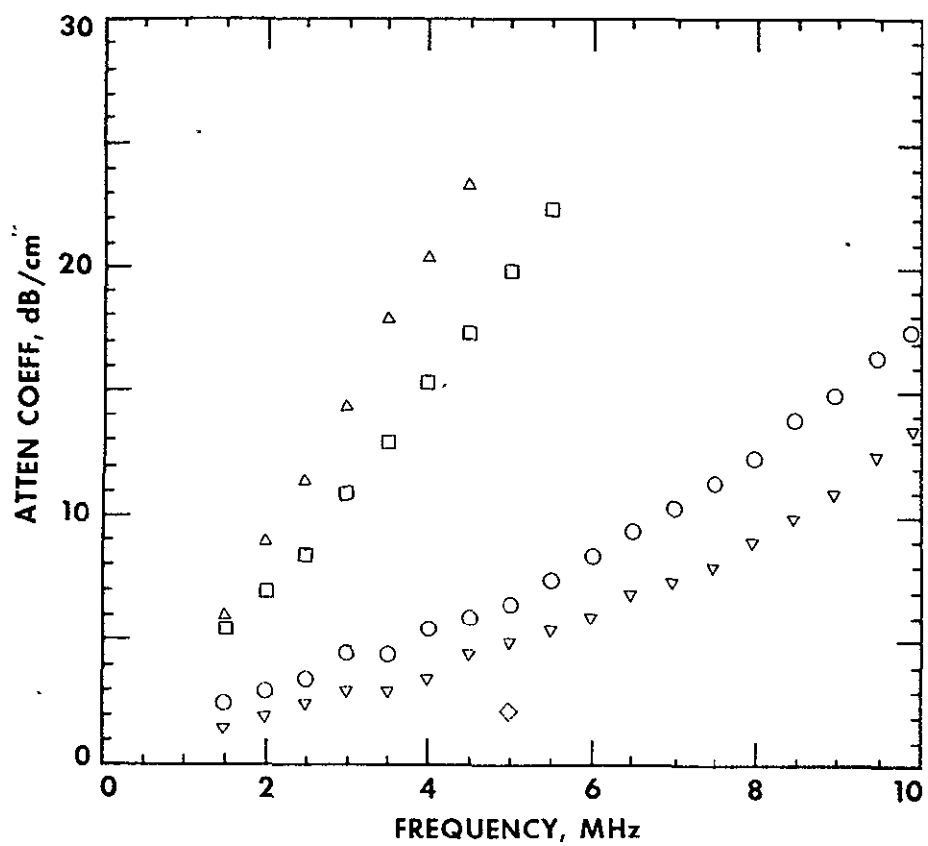
The calibration spectra at 5 dB intervals permit accurate estimation of the attenuation to the nearest 0.5 dB over about a 40 dB range. The nine spectra, from the nine locations on the specimen, were always compared for consistency. Spectra that exhibited multipath interference or abnormally high attenuation were rejected. Five to eight good locations were usually found in a nine-location set of data. The average

of these selected data is presented in Figures 20 to 24. The standard deviation among the averaged spectra varied with the average value and with the particular specimen and temperature. In general it could be represented by:

$$\text{Standard deviation (dB/cm)} = 1.5 + (0.08)(\text{mean attenuation})$$

This variance among locations on the specimen should not be confused with the reproducibility of the data at a given location. When the scanner is removed from a location on the specimen and returned, the attenuation is reproducible to within 1 dB standard deviation.

The attenuation in hog backfat at four temperatures is shown in Figure 20. This specimen was 15 mm thick. The averages are not reported above 4.5 MHz for the 4°C data or above 5.5 MHz for the 20°C data. Above these frequencies some of the spectra exhibited an attenuation beyond the range of accurate measurements (40 dB). Since the attenuation showed much more of a change between 20°C and 37°C than it did between 4°C and 20°C, measurements were also made at 49°C to determine whether the trend would continue. The fact that there is an apparent discontinuity in the temperature dependence is not surprising since fat is known to undergo a phase transition around 36°C and is unnaturally firm at room temperature. Since the attenuation of the backfat was much higher than reported by previous investigators (1), a second specimen was studied. This specimen was subject to careful handling and data acquisition techniques. The data on these two specimens was consistent. This difference in the attenuation of backfat probably reflects the changes in the diet of the hogs since the previous data were compiled in 1956 (1). The hogs used in this study were grain fed and bore a solid white fat. In the 1950's, however, many commercial hogs were garbage fed and produced an oily fat that was less firm and slightly off white. Such a great difference in consistency would be expected to be accompanied by a difference in ultrasonic properties.



▲ 4°C □ 20°C ○ 37°C ▼ 49°C ◇ Goldman & Heuter (1)

Figure 20. Attenuation versus Frequency at Four Different Temperatures in Hog Backfat.

The attenuation of a 12 mm thick specimen of hog liver at three temperatures is shown in Figure 21. The 37°C data is close to the presumed 20°C data of Bamber, et al. (14).

Because we were concerned that the values of attenuation reported here were higher than in our earlier work, three other livers were obtained and slices were studied from the same lobe of each a few hours post mortem. Six attenuation spectra were obtained on each slice. The average of the readings from a given slice varied from the average for another slice by approximately the variance of the readings within a slice. The spread covered the range between the data reported here for 37°C and the data of our earlier work taken at 37°C.

Attenuation in hog spleen at three temperatures is shown in Figure 22. The natural boundaries of the specimen were left intact. The specimen was 9.6 mm thick in the middle, where three readings were taken at each temperature, and 6 mm thick towards either side, where six readings (three either side of the middle) were taken at each temperature. The measured attenuation was divided by the appropriate thickness before averaging.

The attenuation in hog kidney, measured at three temperatures, is shown in Figure 23. These data were taken at nine locations around the region of the pyramids, where the specimen is approximately 19 mm thick. This region includes both cortical and medullary matter. The central region of the organ, which contains the major ducts, and the steeply sloping edges were avoided. The areas studied correspond with those reported in Section VIII (A).

The effect of storage for five days at refrigerator temperatures (5°C) on the attenuation of hog spleen, which was not available for our earlier work was also measured. The average values of the attenuation at 37°C were within 1 dB/cm of those reported for fresh tissue in Figure 22. In both cases the standard deviation was 1.5 dB/cm or less for all frequencies.

C. Human Tissue Studies

Measurements have been made on a number of excised human female breast specimens containing malignant tumors. Most specimens are obtained

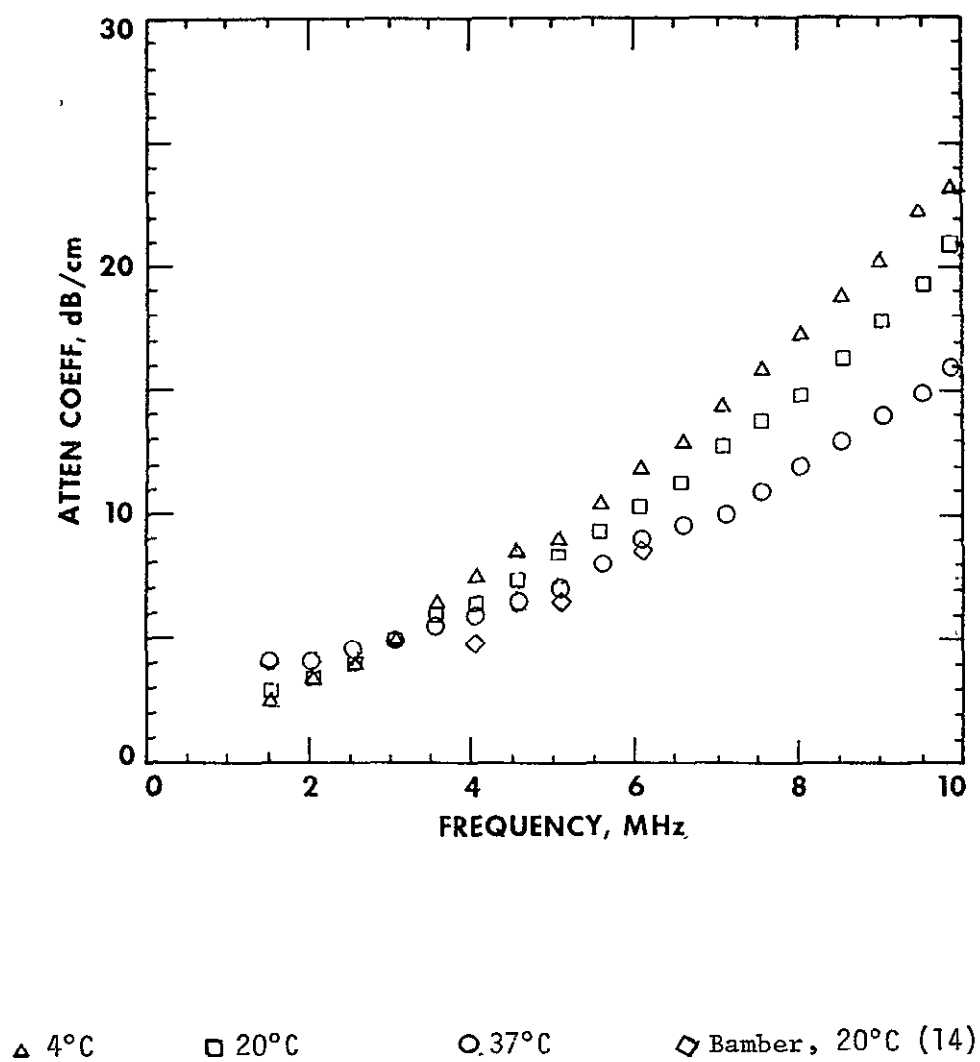


Figure 21. Attenuation versus Frequency at Four Different Temperatures in Hog Liver.

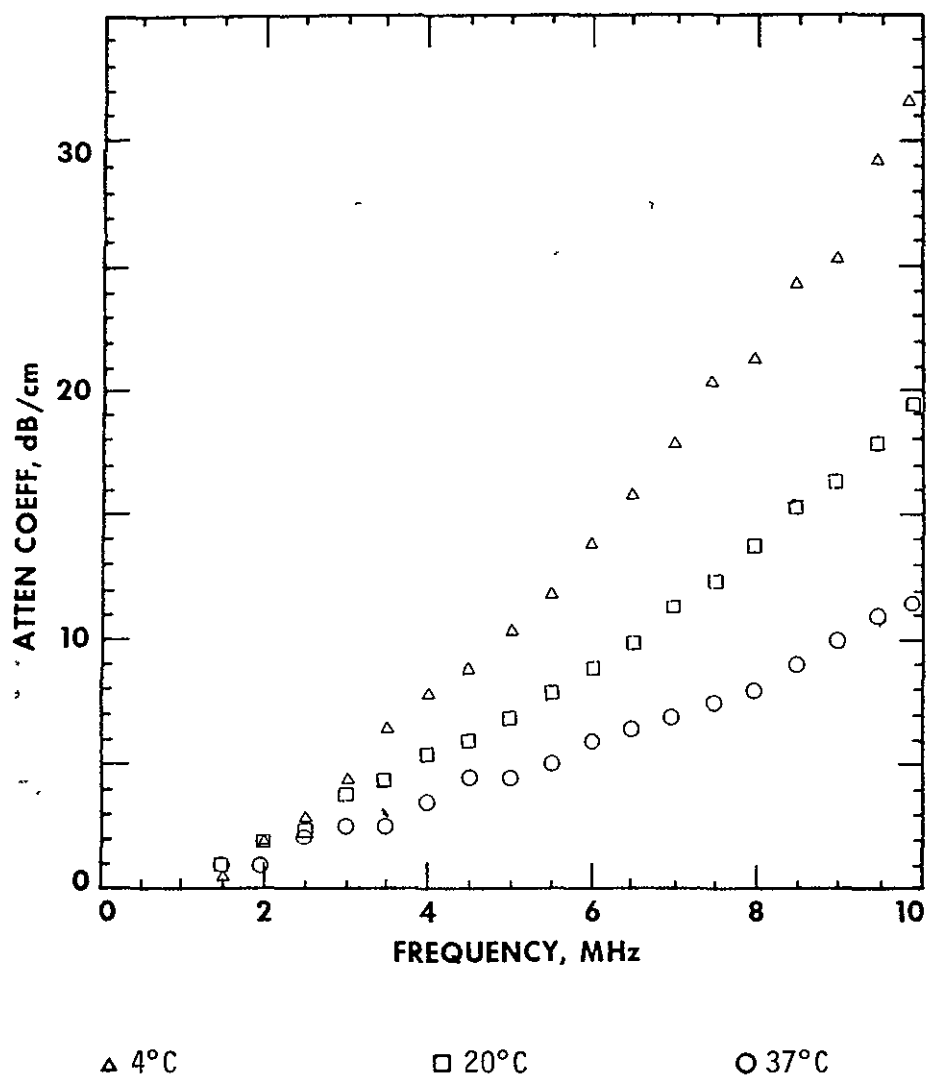


Figure 22. Attenuation versus Frequency at Three Different Temperatures in Hog Spleen.

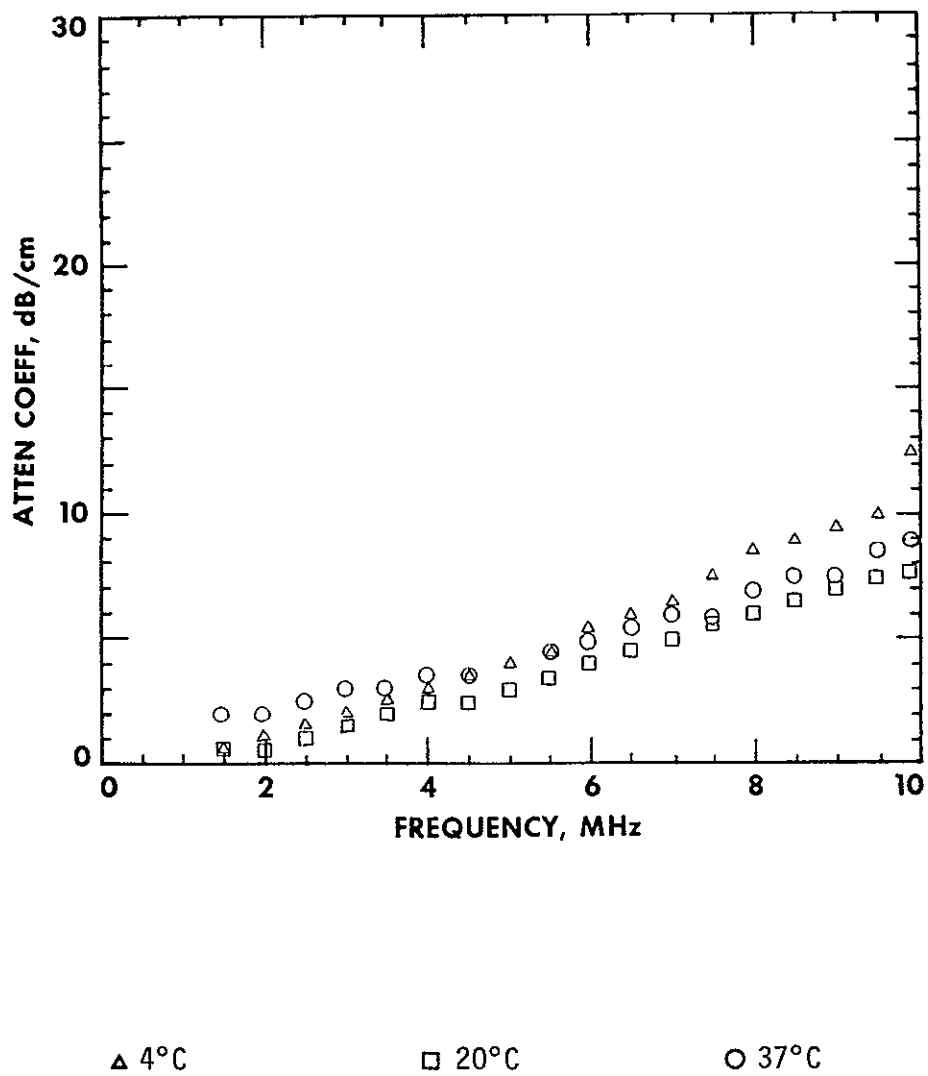


Figure 23. Attenuation versus Frequency at Three Different Temperatures in Hog Kidney.

from women who are above 35 years of age who are the high-risk group. In specimens from the older women there is a high proportion of fat present in the tissue. Even with care in the handling of the specimen it is found that the fat tends to separate from the remaining tissue causing voids which prevent accurate ultrasound measurements from being made. Figures 24 and 25 show two sets of readings where fat separation

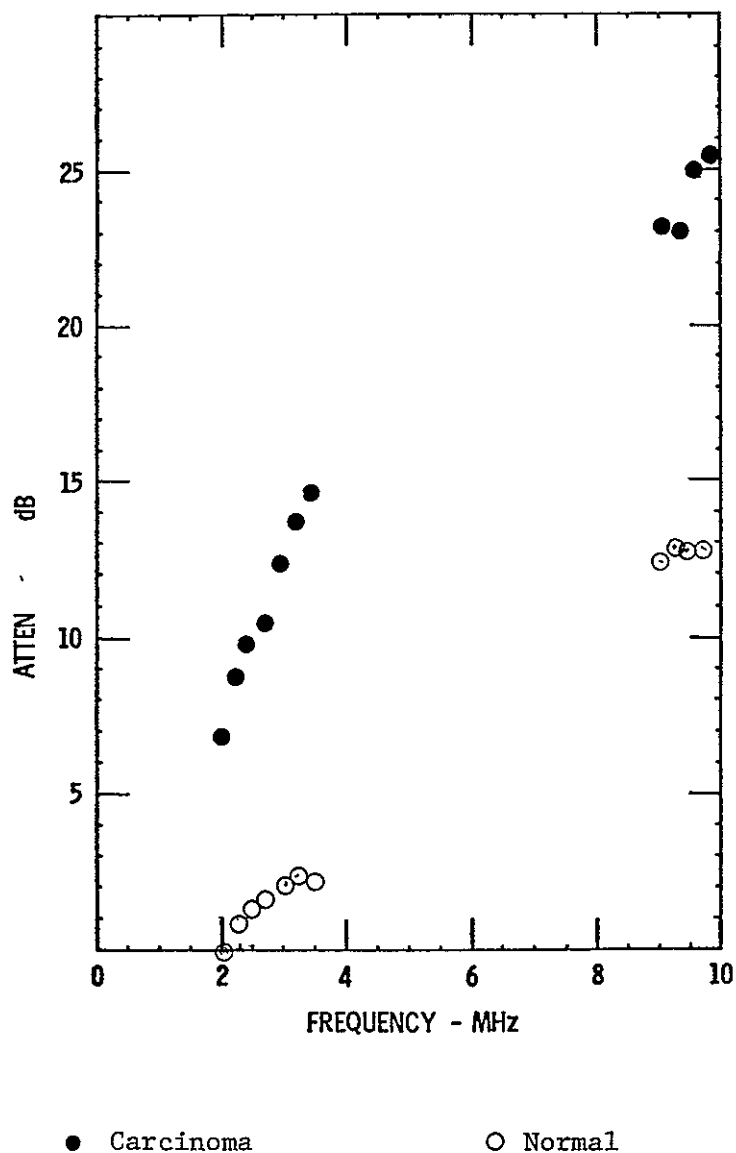


Figure 24. Measurement of Attenuation versus Frequency for an Excised Breast Specimen.

was not sufficient to seriously affect the measurement. In Figure 25 the full spectrum of 1.5 to 10 MHz was recorded. The measurements reported by Calderon et al. (15) and shown on the graph were carried out at 2.25 MHz which is the most commonly used frequency for ultrasonic diagnostic imaging.

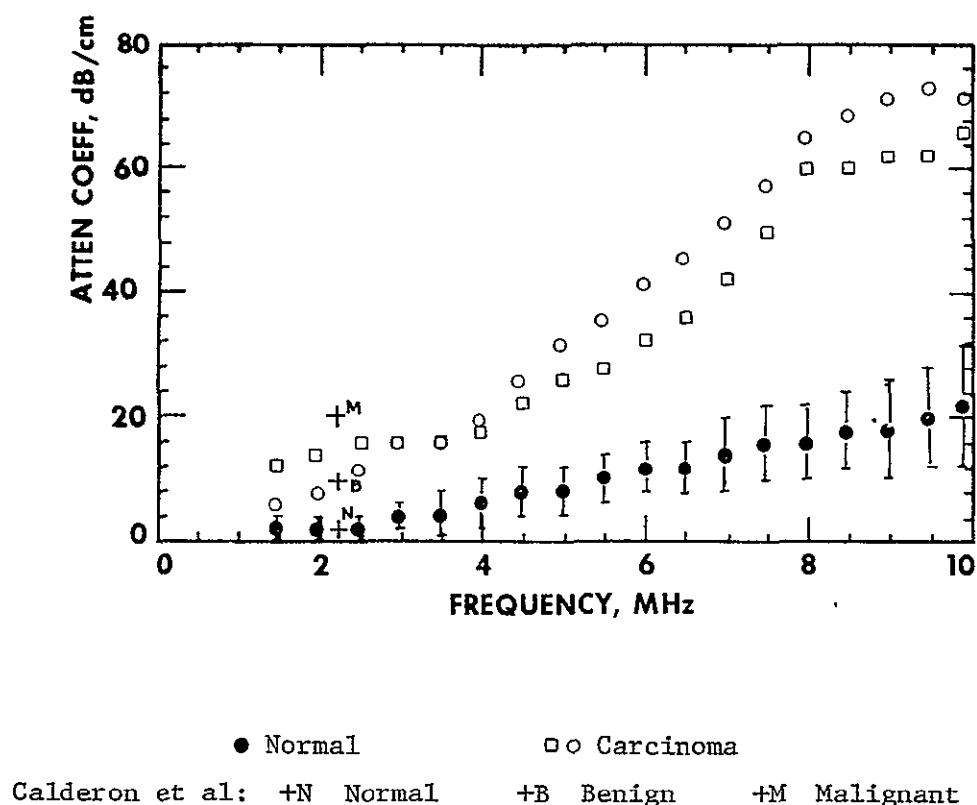


Figure 25. Measurement of Attenuation versus Frequency in Breast Tissue.

In addition to the two primary tumors reported in Figures 24 and 25, a study was made of a carcinoma that had metastasized to the axilla. The tumor was about 1.5 cm across and 0.9 cm thick and was excised during a modified radical mastectomy following an excisional biopsy. The attenuation was measured at several locations on the specimen and the tissue was at 38°C. The average and standard deviation of the attenuation at five locations is shown in Figure 26.

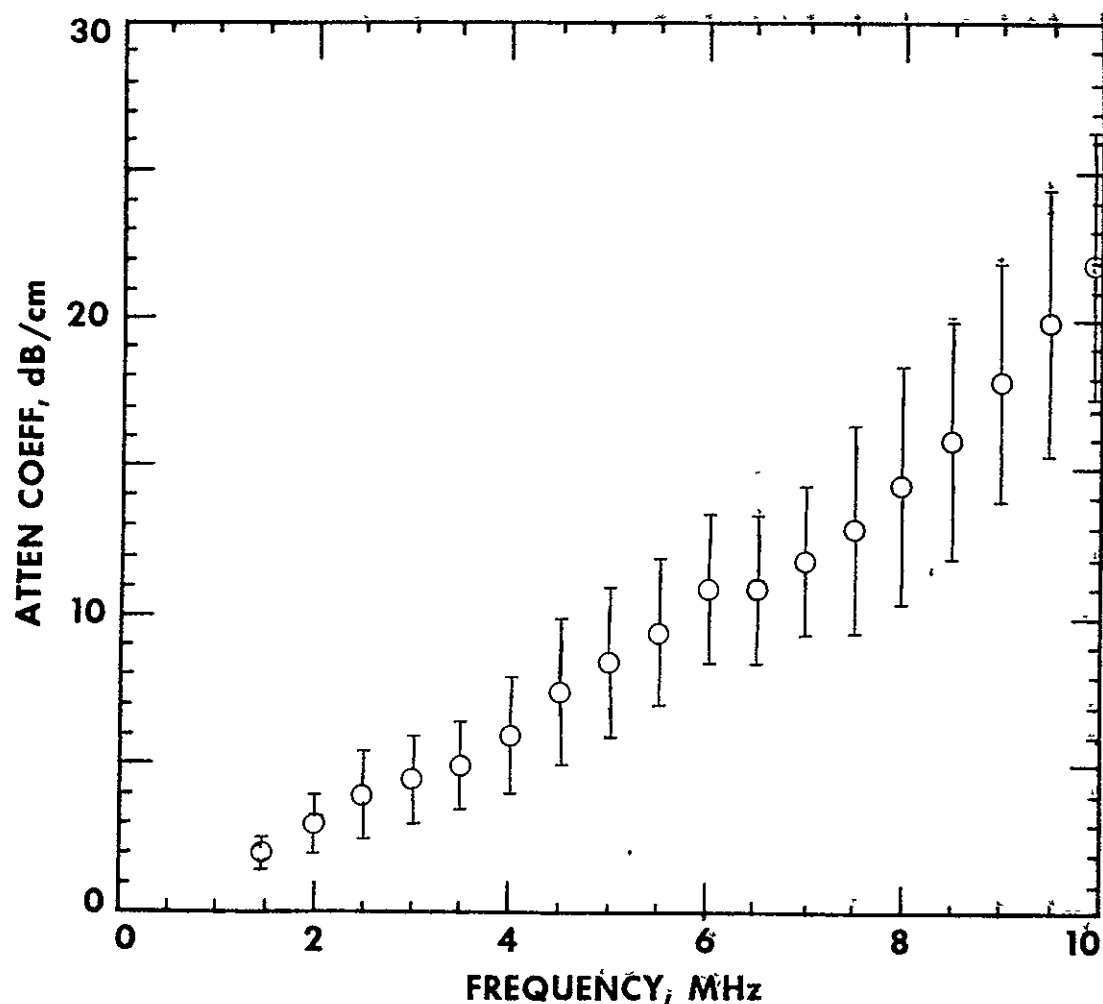
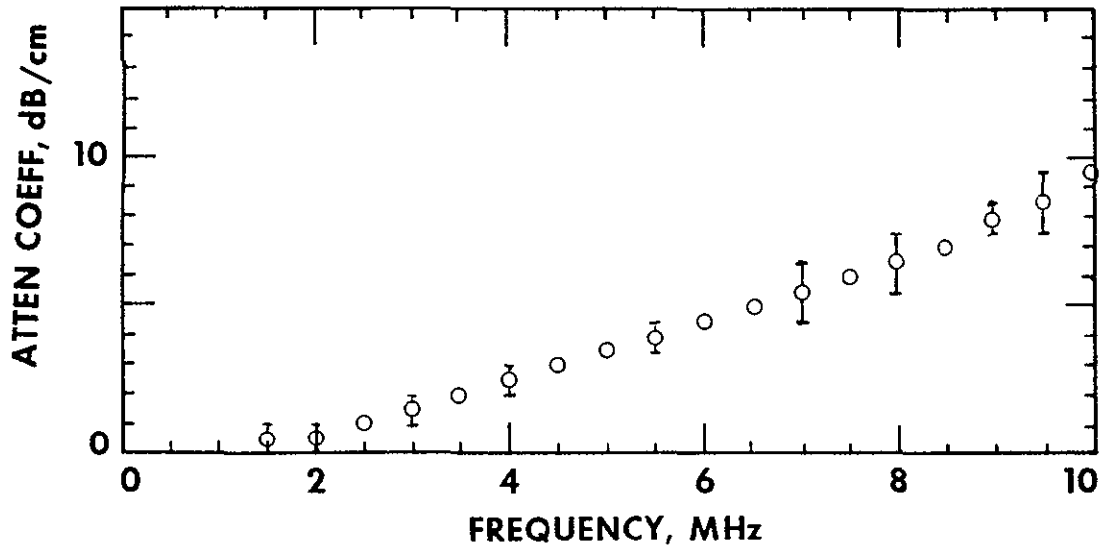
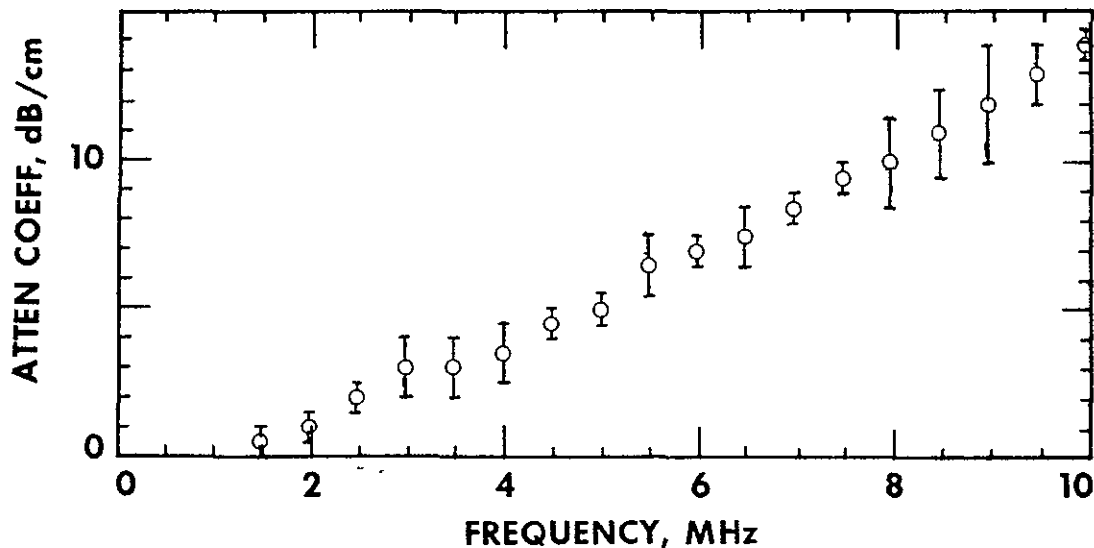


Figure 26. Attenuation versus Frequency for a Metastatic Tumor of the Breast at 38°C.

The frequency dependence of the ultrasonic attenuation of a specimen of human spleen is shown in Figure 27 taken from the cadaver of a person who died of leukemia. It was sliced to a thickness of 6 mm for these studies. The attenuation of the fresh specimen is approximately 1 dB/cm/MHz, which is twice that of normal tissues. Formalin fixation increased the attenuation by about 50%.



(a) Unfixed



(b) Fixed

Figure 27. Attenuation versus Frequency in Leukemic Human Spleen at 37°C. Average of Three Readings. Error bars show standard deviation. (a) Unfixed Specimen, (b) Same Specimen after Formalin Fixation.

The ultrasonic attenuation of a fresh specimen of normal human pancreas is shown in Figure 28. Data taken at five independent locations in the specimen are presented as a scatter diagram rather than being averaged. The shaded circles represent the coincidence of two readings. The specimen was approximately 7 mm thick but was sufficiently irregular to make an exact determination of the thickness at each location studied very difficult. The excised pancreas is an organ with little rigidity. The scatter shown in Figure 28 represents a considerable achievement because of the difficulty in holding and confining this type of tissue.

**SPECIMEN 2028 PANCREAS 37°C FRESH
AVG OF 5 LOCATIONS**

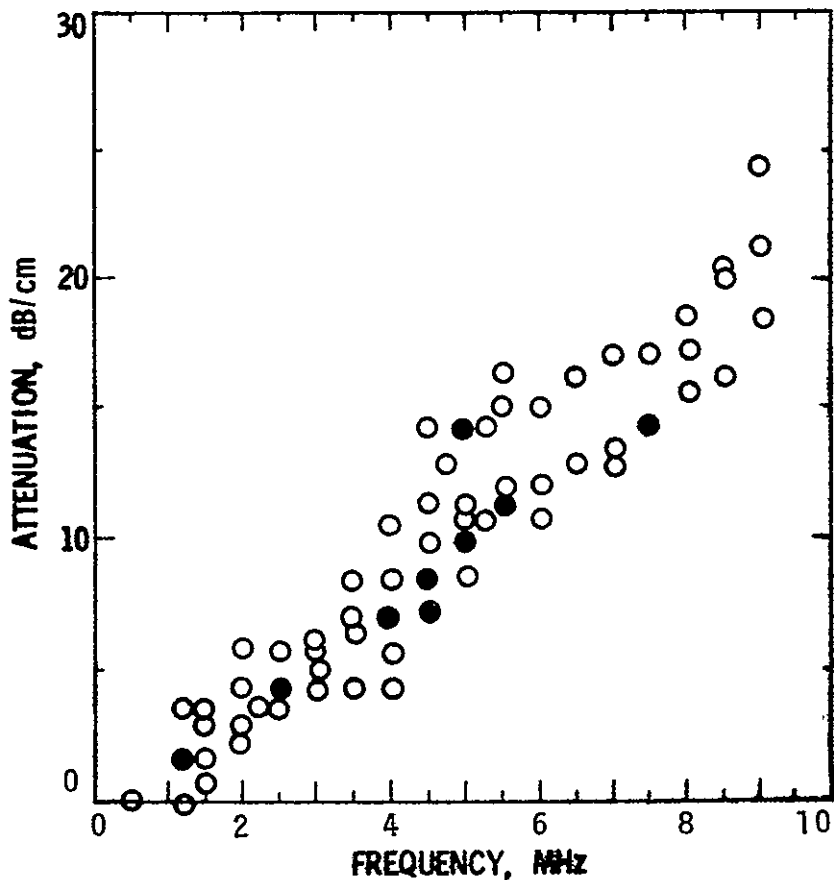


Figure 28. Attenuation versus Frequency in a Human Pancreas.

A small number of studies have been conducted on the effect of fixing tissue in formalin solution. Data are normally taken on human tissues several hours after resection. The cadavers had usually been stored at approximately 5°C for two or three days before autopsy.

The effect of formalin fixing for ten days on a specimen of abdominal fat is shown in Figure 29. Each point represents the average of readings taken at five locations in the specimen. Data were also

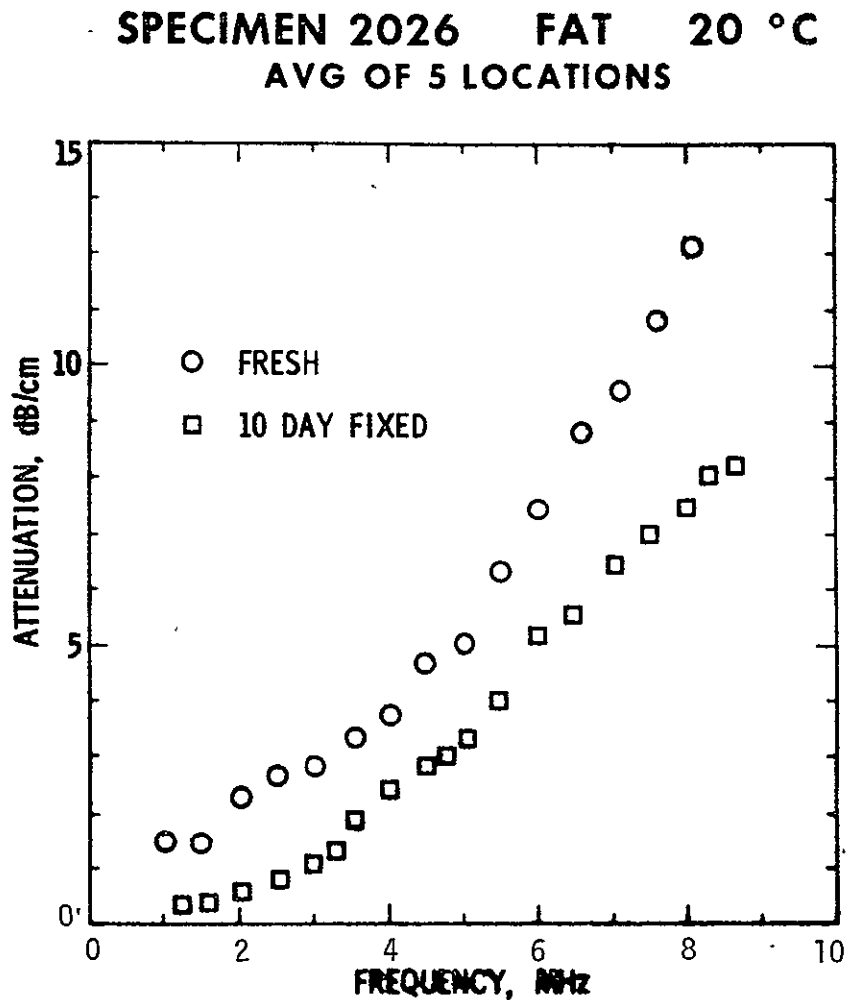


Figure 29. Effect of Fixing on Abdominal Fat.

taken 1 day, 2 days, 4 days, and 7 days after the specimen was fixed. There was no difference (within the accuracy of the measurement) in the ultrasonic attenuation of the specimen after 1 day of fixing and after 10 days of fixing. In previous measurements on breast tissue, it had been observed that both the value of the attenuation and the variance of the readings were increased after fixing. The post-menopausal breast tissue studied had a high proportion of fat so it was anticipated that a similar effect would be seen in the abdominal fat specimen. From Figure 29, however, it can be seen that fixing has decreased the attenuation and has not affected the variance of the data appreciably.

The effect of formalin fixing on a specimen of a fatty and cirrhotic liver is shown in Figure 30. For this particular specimen

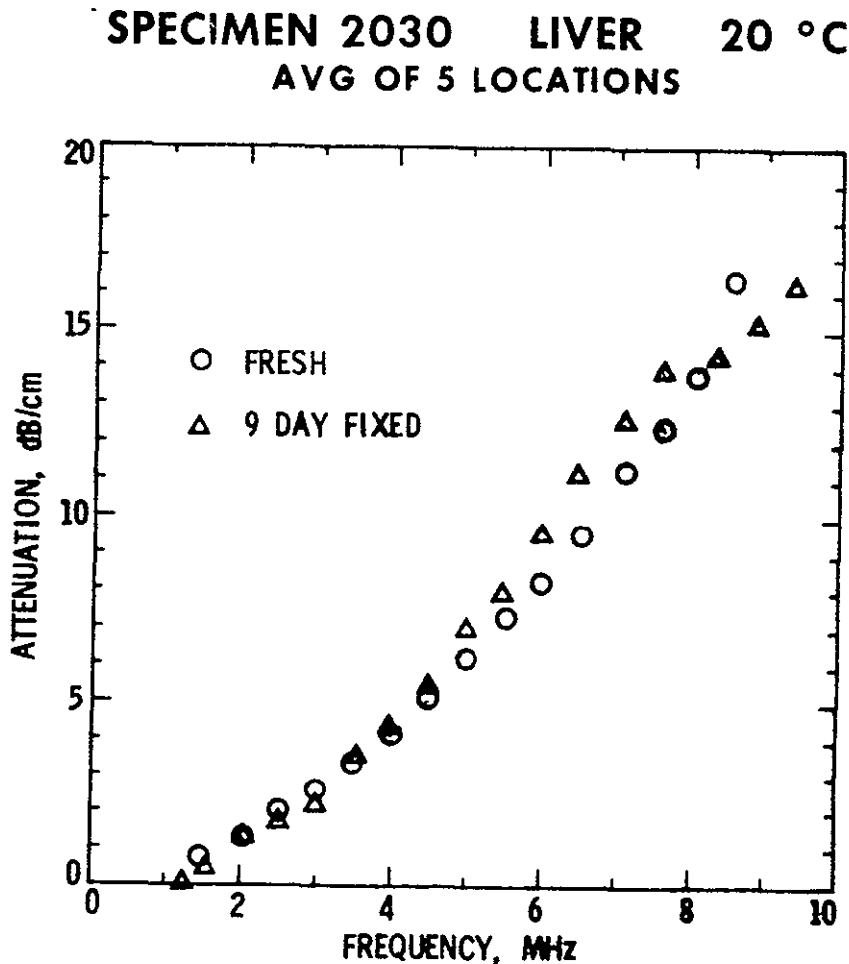


Figure 30. Effect of Fixing on a Liver Specimen.

the formalin fixing did not make any discernable difference in the ultrasonic attenuation. The accuracy of these data is about ± 1 dB, so the difference in these curves is judged to be not significant. Figure 31 shows the effect of fixing upon an acute fatty liver. Two

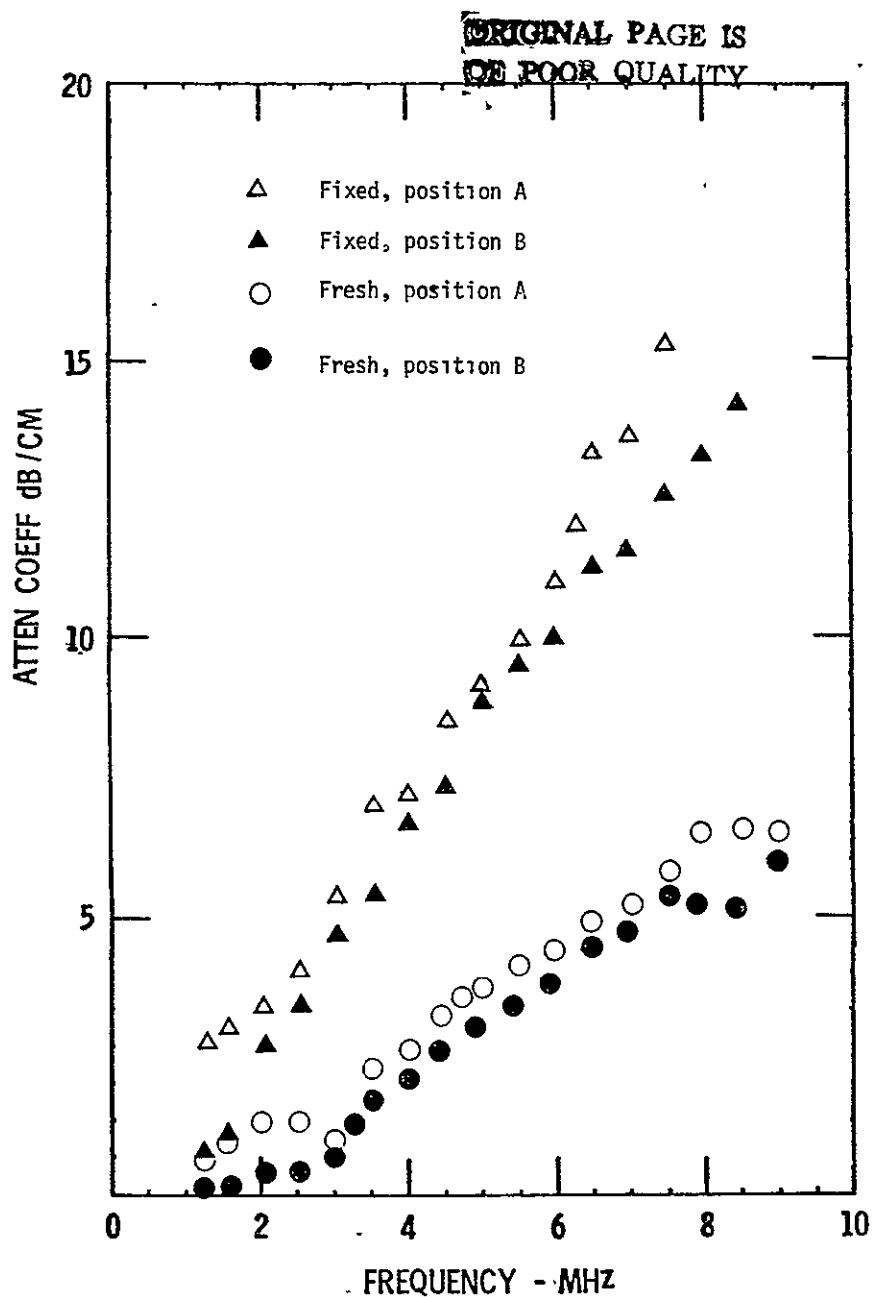


Figure 31: Effect of Fixing on an Acute Fatty Liver.

sites were selected. The difference in the sites were probably due to the different proportions of fat at that position in the liver. Formalin fixing raised the attenuation for both regions about equally.

Measurements on human liver as a function of temperature have been made throughout the program. The first measurement was made on a fatty, cirrhotic specimen and is shown in Figure 32. These data at 20°C agree

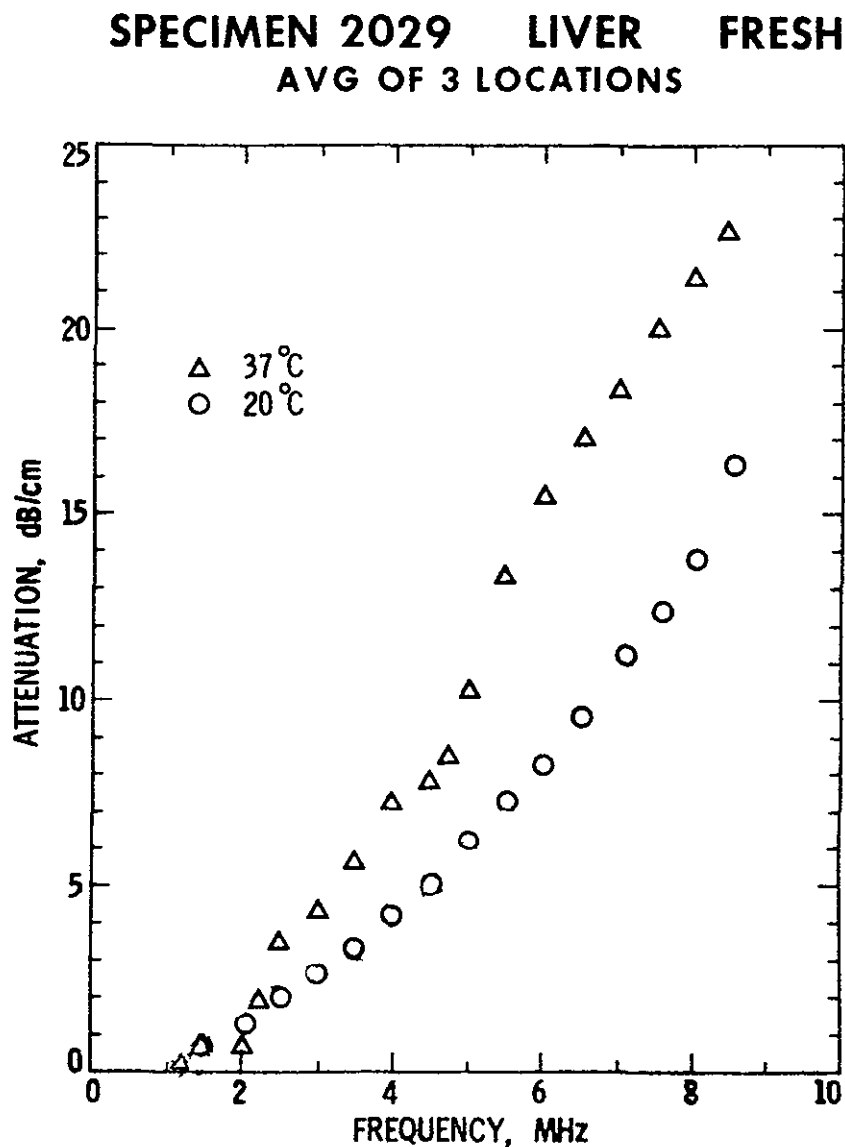


Figure 32. Early Measurements of Attenuation versus Frequency at Two Temperatures on a Fatty, Cirrhotic Liver.

with the information for a neighboring slice of the same liver shown in Figure 30. At the time that the experiment was carried out, the system had not been modified to include the digital synthesizers and a primitive temperature control system was used which maintained the temperature within about $\pm 2^\circ\text{C}$. Later measurements on a normal liver are shown in Figure 33 and on a fatty liver in Figure 34. In these measurements

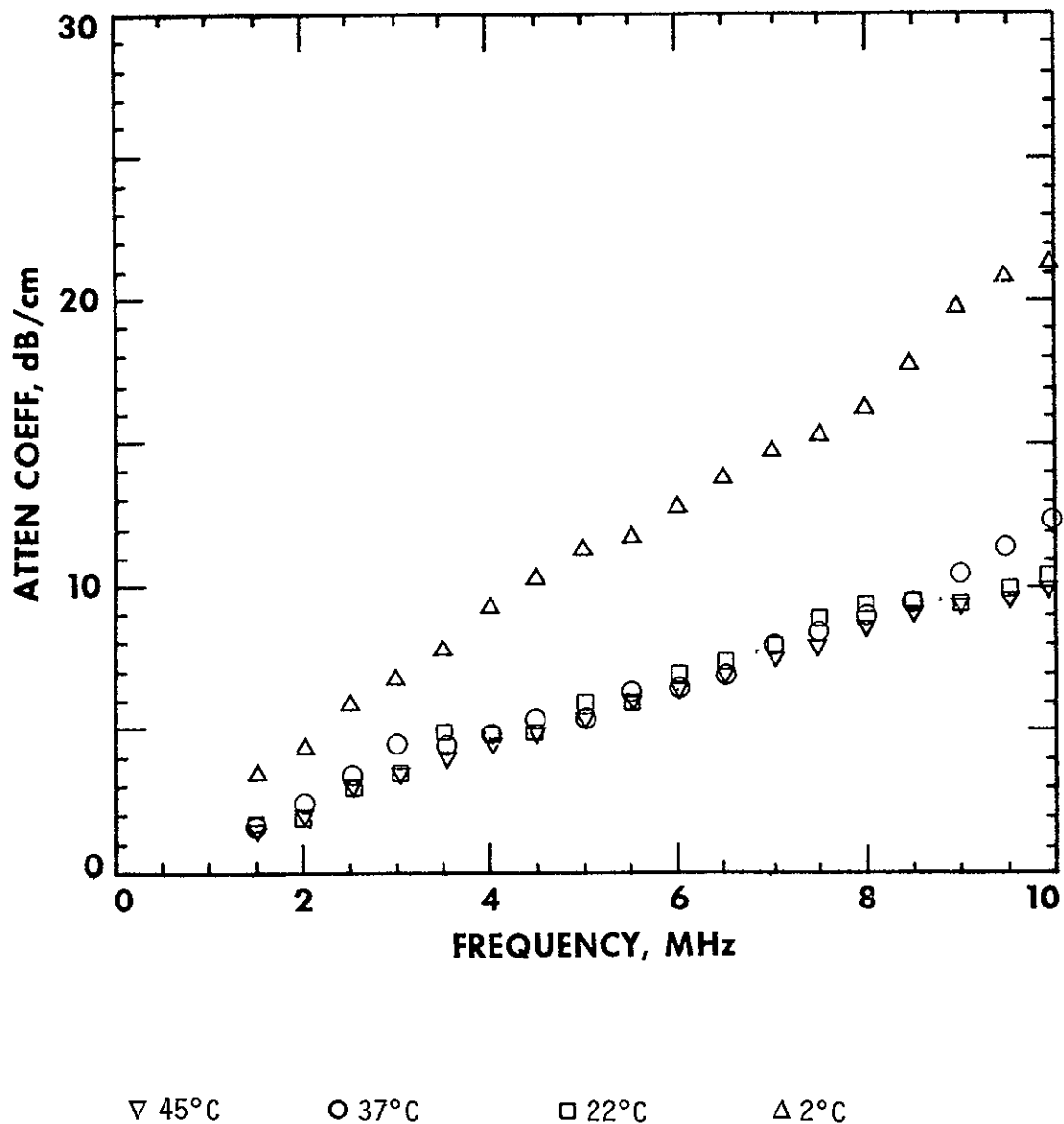


Figure 33. Attenuation versus Frequency as a Function of Temperature on a Normal Liver (average of seven readings).

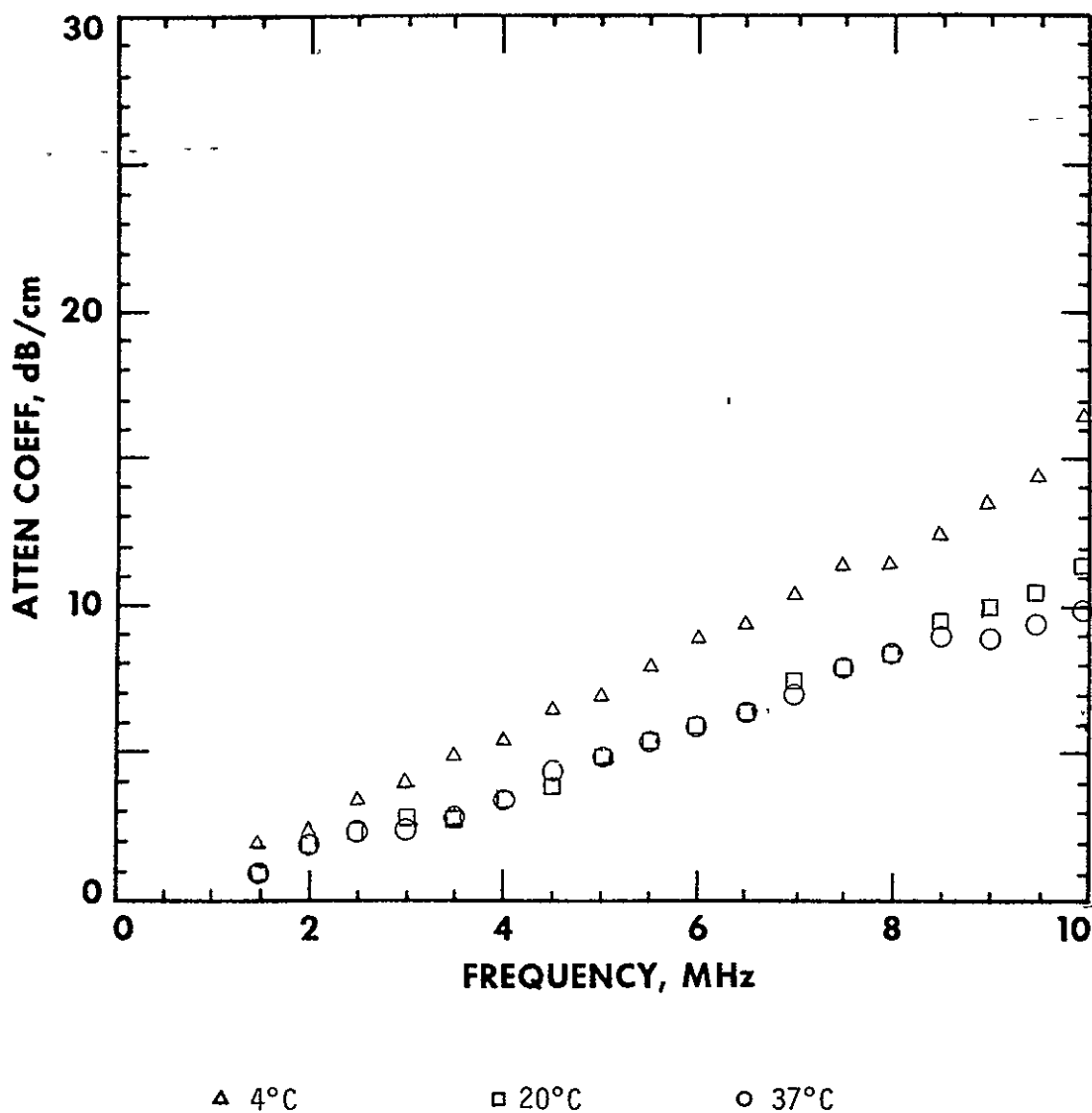


Figure 34. Attenuation versus Frequency as a Function of Temperature on a Fatty Liver (average of nine readings).

the final system was used and a temperature controller accurate to about $\pm 1^\circ\text{C}$ had been installed. Note that the attenuation at 37°C in both livers is about the same and there is little change in attenuation at temperatures studied until very low temperatures are reached. As the temperature was reduced to 2° and 4°C in Figures 33 and 34 respectively a higher attenuation was recorded. The standard deviation of these multiple readings

corresponded with the values given earlier, i. e.,

$$\text{Standard deviation (dB/cm)} = 1.5 + (0.08)(\text{mean attenuation}).$$

Further measurements were taken on specimens of cirrhotic human liver. These measurements are shown in Figures 35, 36 and 37. In all cases, the attenuation markedly increases at 2° or 4° C. In Figure 36

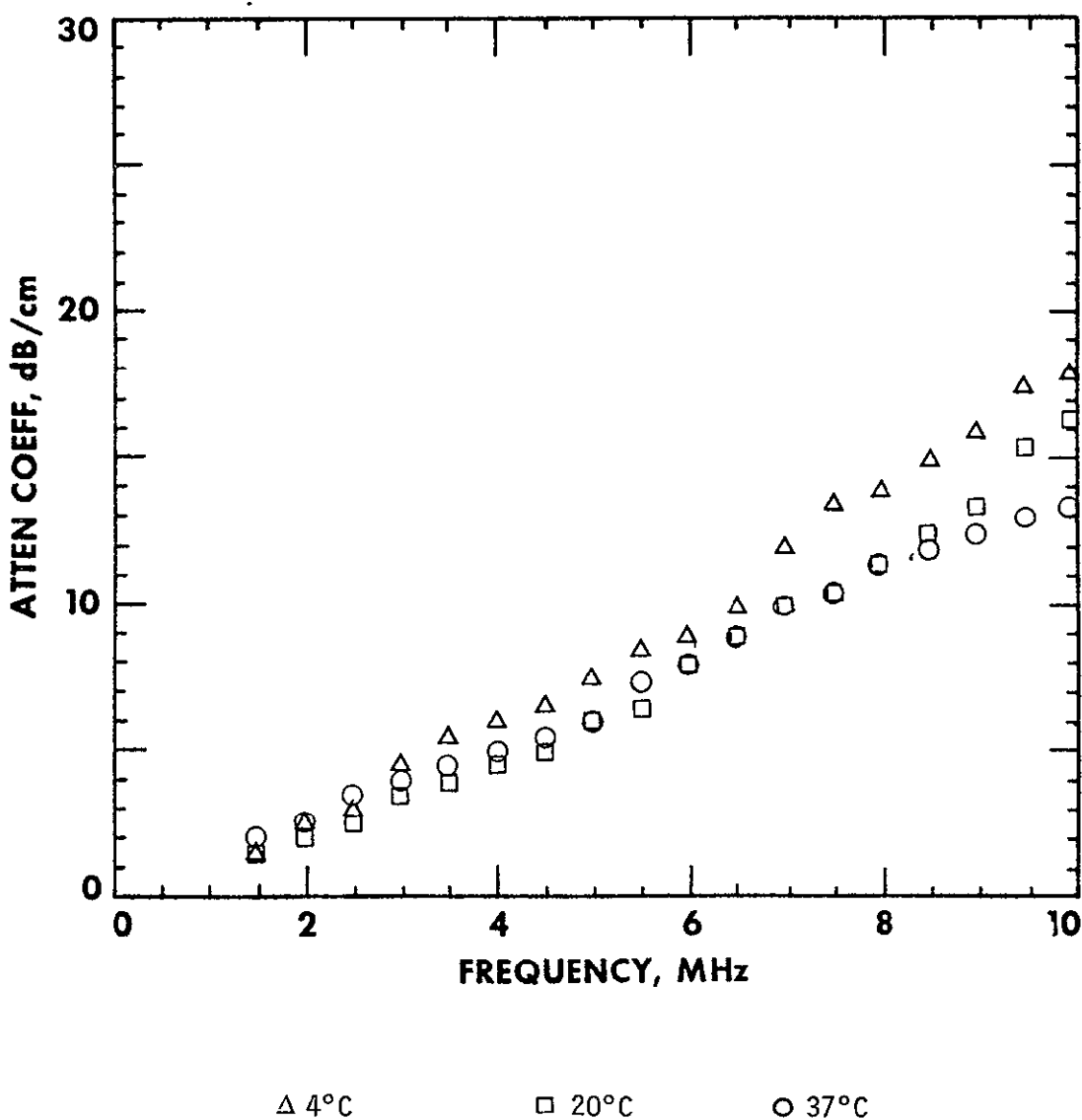
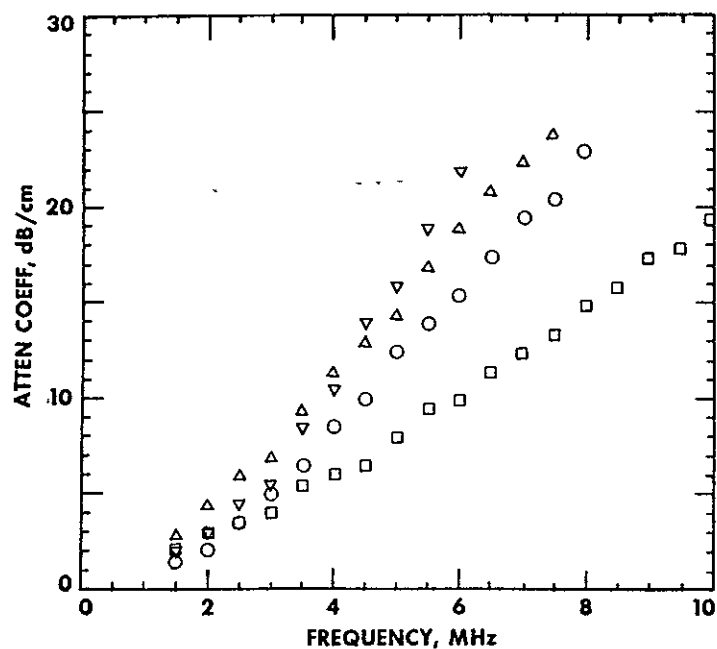


Figure 35. Attenuation versus Frequency as a Function of Temperature in a Cirrhotic Liver (average of nine readings).



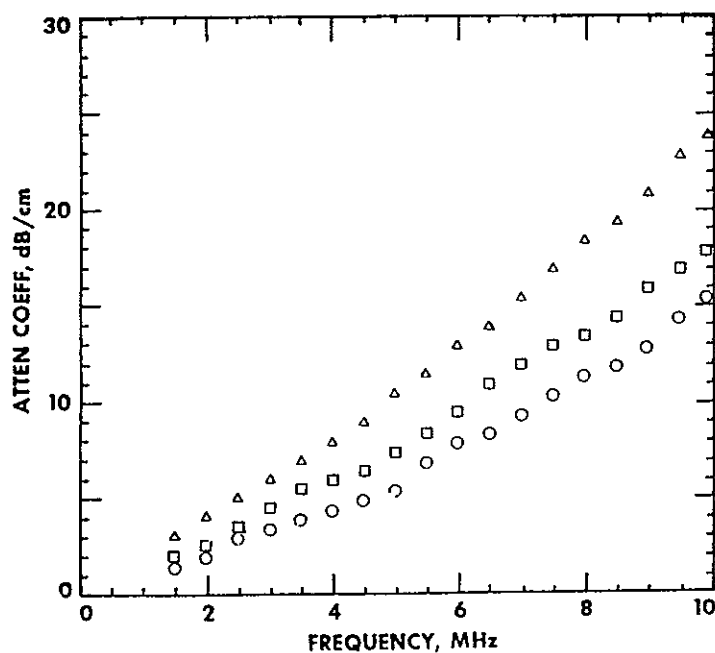
▽ 45°C

○ 37°C

□ 21°C

△ 2°C

Figure 36. Attenuation versus Frequency as a Function of Temperature in a Second Cirrhotic Liver (average of five readings).



△ 4°C

□ 20°C

○ 37°C

Figure 37. Attenuation versus Frequency as a Function of Temperature in a Third Cirrhotic Liver (average of five readings).

there is also an increase in attenuation at 45°C. Although gas bubbles were not observed, the specimens were exposed to the higher temperatures for less than two hours, so it is possible that gas evolution could be contributing to the higher attenuation observed at the higher temperatures.

The effects of temperature on a fixed specimen of cirrhotic liver is shown in the final Figure 38. This is the same specimen used in the

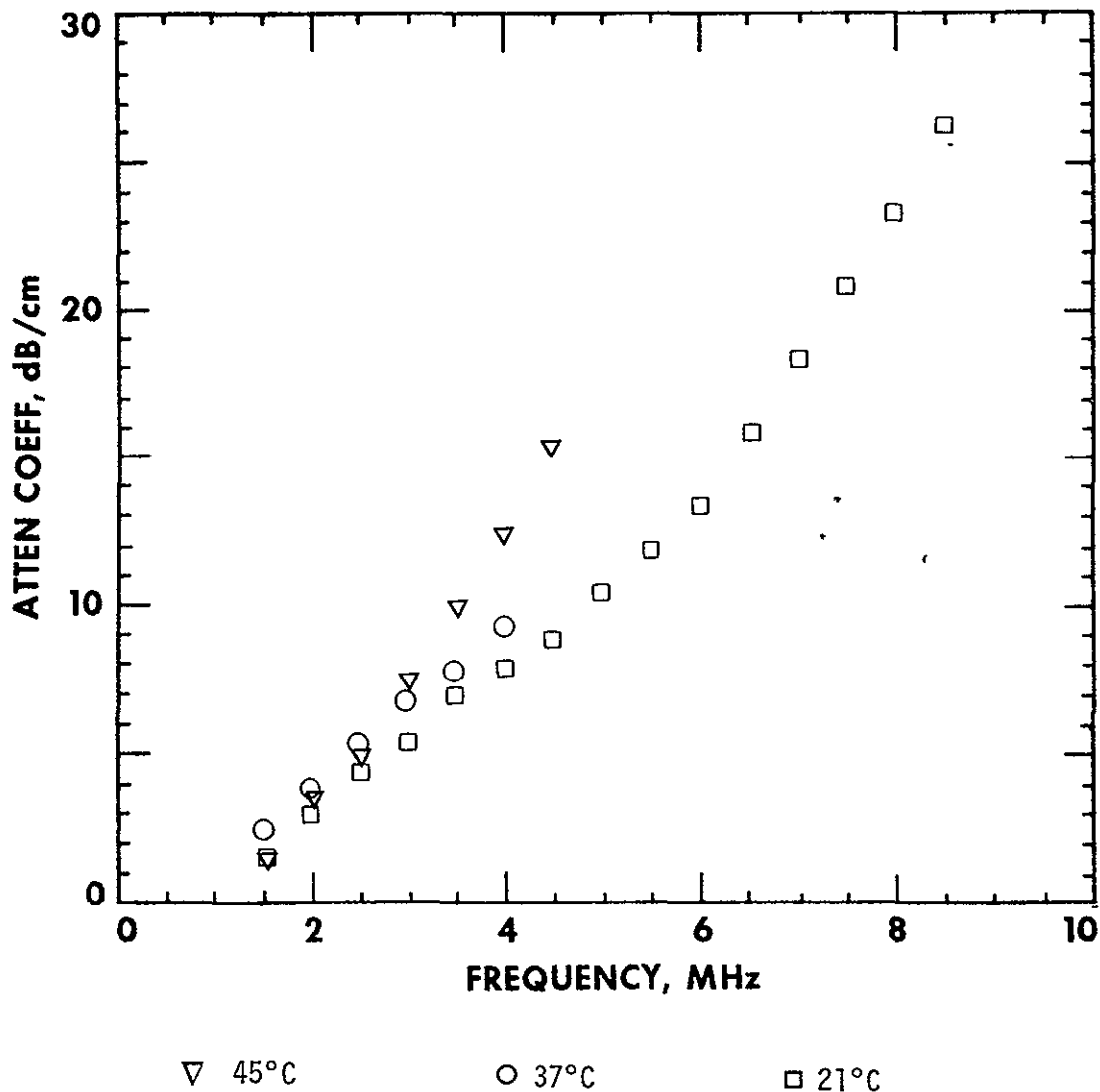


Figure 38, Variation in Attenuation with Temperature for a Cirrhotic Liver. Readings taken on the same Liver as Figure 36 after it had been Formalin Fixed.

experiments shown in Figure 36. Once again, there is an increase in attenuation at the highest temperature (45°). The trend of a higher attenuation at lower temperatures is consistent with the observation on hog specimens and may suggest macromolecular relaxation at frequencies below 1 MHz. The higher attenuation sometimes observed at higher temperatures cannot be explained by a simple relaxation process, however. Experiments in which the ambient pressure is varied could confirm or refute the possible effects of autolysis or determine whether release of dissolved gas is involved. Care must be taken with such procedures to avoid damaging the specimens by the bubbles produced when the pressure is lowered.

D. Measurements from 1.5 to 17.5 MHz.

The equipment in its present configuration is routinely used to perform measurements over the frequency range of 1.5 to 9.9 MHz with great speed and accuracy. The lower frequency limit is set by the transducers and, although it could be reduced to about 0.2 MHz with the appropriate transducers, there is little interest in this frequency range for tissue characterization, and the high frequency data could not be obtained with the same transducers. The upper limit is set by the Dana synthesizers, which cover 0 to 10 MHz. Simple heterodyne techniques would enable these synthesizers to cover any 10 MHz range, such as 10 to 20 MHz or 20 to 30 MHz.

The capability of the equipment to cover a more extensive frequency range is demonstrated in Figure 39. In this implementation the Panoramic SPA-3 Sweeping Spectrum Analyzer was used with its G-6 Companion Generator unit. The G-6 provided the sweep which tracked the receiver frequency with a selected offset, to produce a TDS system. Highly damped 10 MHz probes were used. Above 10 MHz the transducer response falls while the specimen attenuation is increasing. In spite of the much reduced signal at these higher frequencies, reasonable data was obtained up to 17.5 MHz. These data were acquired in four segments, and the overlap of these segments provided a check on the technique. Fixed specimens were used since it was only desired to demonstrate the technique.

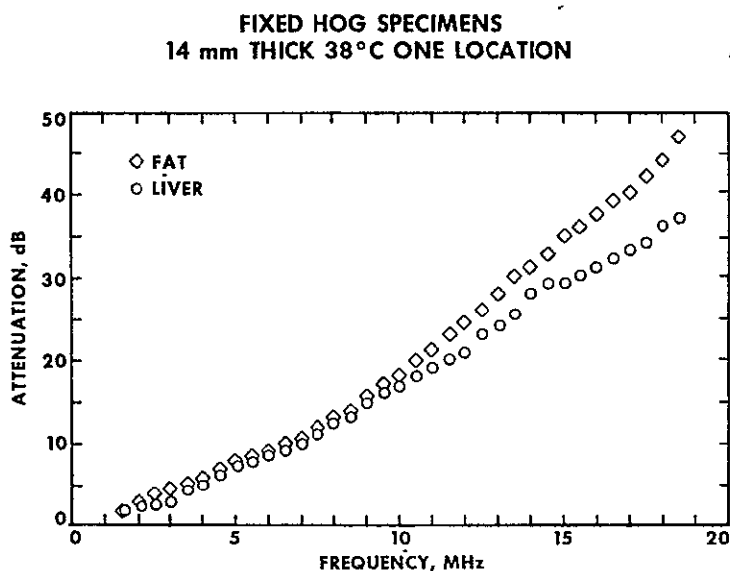


Figure 39. Measurement of Attenuation versus Frequency on Hog Specimens over Range 1.5 to 17.5 MHz.

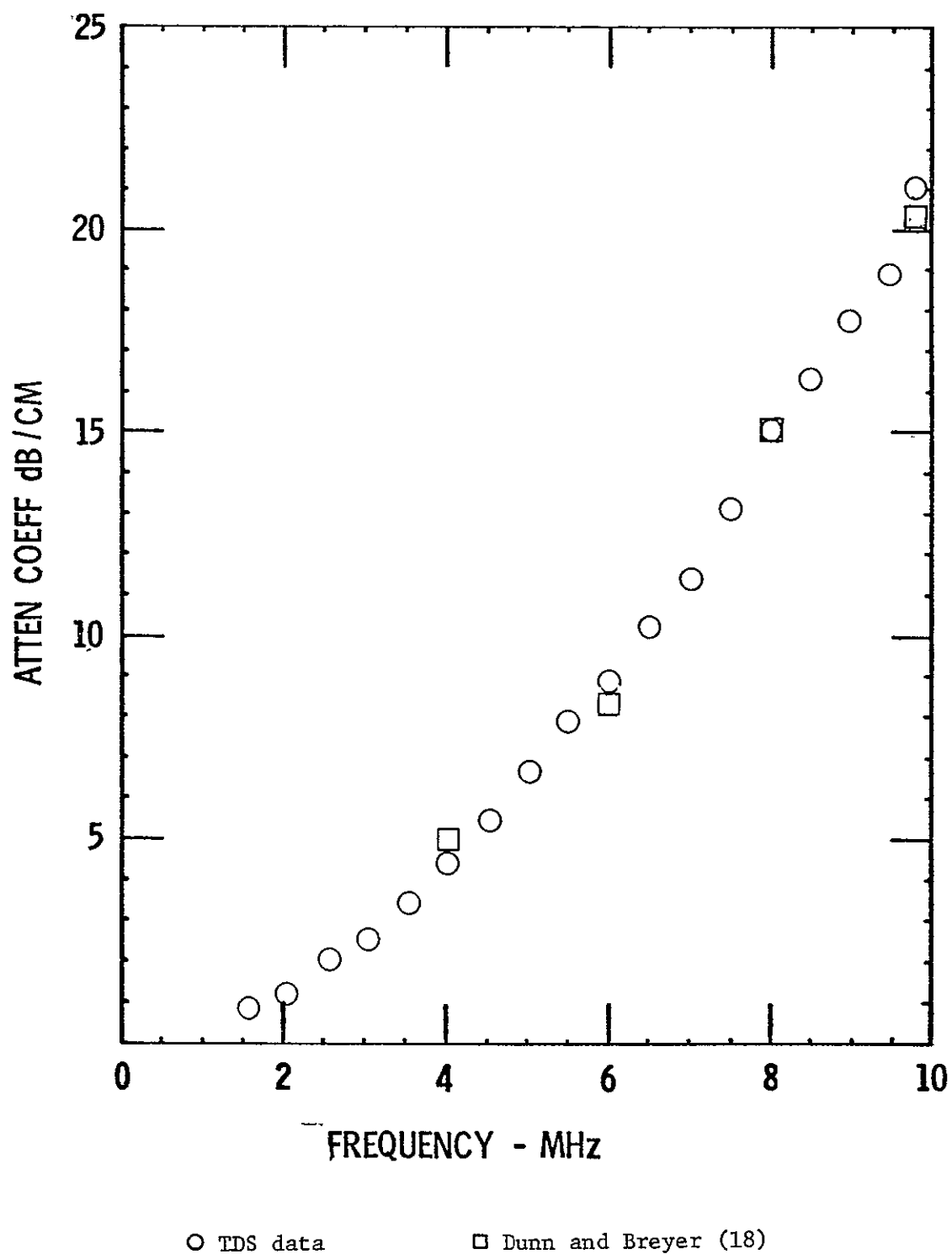


Figure 40. Comparison of Measurements on Castor Oil taken on the TDS System with Data of Other Investigators.

IX. CONCLUSIONS

The work carried out in the course of this task was divided into three parts; improvement of the instrumentation, tissue handling, and ultrasonic measurements on tissue.

During the task the Time Delay Spectrometer was upgraded considerably by the purchase of the two frequency synthesizers. This improved the accuracy of the measurements and produced a precision system. Considerable time was spent in this upgrading including electronic design and fabrication and the development of precise controls for the scanner mechanism. In addition, a great amount of effort was expended in transducer measurements, in transducer alignment problems, and in obtaining reproducible measurements.

Apart from the advantages of the TDS system for measurements over the frequency spectrum, the frequency synthesizers also allows transmission or reflection images to be made over a selected frequency range. This capability was not used in this work but images may prove to be useful for tissue identification later.

It is apparent that to utilize the capability of the instrumentation fully it is desirable to digitize the output and use a computer to perform the function of selecting the required data for any particular task. In this way a stored record of the complete ultrasonic signature of a tissue may be obtained for later retrieval. This improvement in the system has been designed to be used for the detection and diagnosis of breast cancer.

The difficult problem of tissue handling consumed a great amount of time on this program. The Jet Propulsion Laboratory has no clinical or animal facilities and all tissue has to be obtained from local hospitals. The difficulties of obtaining human tissue less than 24 hours post mortem precluded a study on the effects of aging on human tissue and so hog tissue was substituted.

The first responsibility of a clinical pathologist is to the determination of pathology using the established methods. For this reason,

it was sometimes difficult to obtain adequate supplies of human tissue containing pathological sections. This research group has enjoyed excellent relationships with the hospital staffs which enabled us to obtain the required specimens that were otherwise unavailable.

The major series of measurements reported here as Figures 11 through 15 are summarized in Figures 16 through 19. It is seen that the effect of aging on fresh tissue stored at refrigerator temperatures is a general reduction in the attenuation as a function of frequency as autolysis takes place. When the tissue is formalin fixed, there is a small increase in attenuation. The magnitude of these effects is not great. This means that measurements taken on tissue under varying degrees of freshness will be reasonably representative of that type of tissue in general.

Throughout the measurements a wide variance of the data due to the difference of acoustical characteristics of the specimen at different locations was found. This is not the result of the experimental techniques but is due to the intrinsic properties of the tissue. A typical standard deviation for a soft tissue specimen measuring about 10 dB/cm at any particular frequency was about 2.3 dB/cm.

This argument indicates that attenuation can be used as a signature in the detection of small pathologies if the attenuation (in dB) of the lesion differs from that of the surrounding tissue by a factor of at least two. Earlier reports (15, 16, 17) indicate this to be the case.

Data taken at only one point on the specimen cannot be considered as representative without serious qualification. In the past such data have been published by many workers and, while it has served to indicate that an effect is there, it cannot be taken as a representative quantification of the effect. Such data have, however, provided a useful indication to guide and motivate other researchers. For true quantification both the mean and the variance should be presented to give an idea of the true value of the data and the significance of the claimed trends. For much of the data reported here 9 separate locations were measured.

One can expect that some locations on the tissue will produce abnormal attenuation due to the presence of ducts and other gross irregularities which give rise to refraction errors and multipath effects. In the case of hogs, it is believed that the feeding regimen

affects the consistency and hence the ultrasonic properties of an apparently simple tissue such as backfat. The dietary component of unsaturated vs saturated fat could also have a dramatic effect on the ultrasonic properties of human fat.

Judgment must be exercised in selecting the spectra to be averaged. This judgment may be either in the way of common-sense human judgment, based on a knowledge of the possible effects present, or could be implemented with a concise algorithm, if mechanized objectivity is desired. The greater portion of this variance may be attributed to the local variation of the acoustic properties of the specimen. This conjecture is supported by the fact that, for any tissue, the standard deviation of the tissue attenuation is roughly proportional to the mean of the readings. If this is indeed the case, then this variation presents a fundamental limitation to the precision to which the attenuation of tissue can be measured by any methodology or can even be defined. Averaging over more readings or using a transducer with less spatial resolution would allow measurements with less variance to be reported, but measurements taken with low resolution are of limited use in clinical medicine.

Study of living or of perfused organs would provide data more representative of the natural state to determine whether there is a disproportionate change in ultrasonic properties in the first few hours post mortem. Such studies are difficult or impossible for some organs since the complex shape of the tissue boundaries would complicate the measurement and cause problems in taking accurate data.

Since, at least for the tissue studied, an 18°C change in temperature in the vicinity of body temperature is seen to give a maximum change of a factor of 1.6 in the attenuation of 9 MHz, a 1°C change will result in an average 3% change in attenuation. This is of the order of the other uncertainties of the data indicating that maintaining the temperature within 1°C is acceptable. Maintenance of the temperature within about 0.2°C or 0.5°C would be preferable, however, since it would reduce the effect of the temperature well below the other uncertainties that affect the attenuation data. The temperature dependence of attenuation is most noticeable at higher frequencies.

In the conventional diagnostic frequency range the effect is barely distinguishable from the measurement uncertainties.

Most of the tissues studied show a substantial change of attenuation with change in temperature. Scattering due to acoustic impedance variation within the specimen and conversion of acoustic energy into heat are probable major contributors to the attenuation of sound which is observed. Significant acoustic losses in fluid constituents are caused by shear viscosity and bulk viscosity. Shear viscosity is due to frictional forces during relative motion between adjacent liquid layers. Bulk viscosity, due to molecular rearrangements taking place during the sound wave cycle, is even more important than shear viscosity in a fluid medium, or in a medium which is substantially of fluid characteristic.

The time required for molecular reordering in response to changing pressure is called the relaxation time. The loss of acoustic energy depends on the relaxation time of the process, compared to the period of the sound wave. It is a property of a relaxation process that the attenuation is proportional to the square of the sound wave frequency below the reciprocal of the relaxation time, and tends toward a constant for operating frequencies above this relaxation frequency.

Since relaxation processes can contribute to absorption and dispersion within an acoustic medium, such processes may account in part for the attenuation which we observe. The extent to which relaxation mechanisms contribute to the observed attenuation is an open issue at this time, but the effect should not be discounted.

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